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CONTENTS OF PREVIOUS NUMBER

MARCH, 1926. NUMBER 3

Experimental Renal Insufficiency: The Effects of High Protein Diet in the Presence of Low Renal Function on the Kidneys, Aorta and Liver; Changes in the Blood Pressure and Concentration of Blood Metabolites. Hilding Anderson, M.D., Duluth, Minn.

I. Controls on Normal Diet.
II. Protein Diet Experiments.

Hemochromatosis and Chronic Poisoning with Copper. F. B. Mallory, M.D., Boston.

Primary Carcinoma of the Liver. Virgil S. Counseller, M.D., and Archibald H. McIndoe, M.B., Ch.B., Rochester, Minn.

The Effect of Liver Damage on Cholecystography in Dogs by the Use of Sodium Tetra-Iodophenolphthalein. B. M. Fried, M.D., and L. R. Whitaker, M.D., Boston.

The Relation of Thrombocytes to Hemorrhagic Diathesis. I. W. Held, M.D., New York.

Carbon Monoxid Poisoning: A Comparison of the Present Methods of Treatment. D. C. Walton, M.D.; W. A. Eldridge, Ph.G.; M. S. Allen, B.S., and M. G. Witherspoon, B.S., Edgewood, Md

The Enzymic Activity of the Duodenal Contents Following the Ingestion of Pancreatin. A. H. Aaron, M.D.; J. V. Wadsworth, M.D., and H. C. Schneider, M.D., Buffalo.

The Value of a Starch-Iodin Reaction as a Test of Pancreatic Function. George Morris Piersol, M.D.; H. L. Bockus, M.D., and Harry Shay, M.D., Philadelphia.

Some Metabolic Aspects of Calcium Therapy. A. P. Briggs, M.D., St. Louis.

Effects of Intravenous Injections of Acriflavine in Sepsis. C. F. Tenney, M.D., and Joseph Lintz, M.D., New York.

Book Reviews.

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Archives of Internal Medicine

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THE MECHANISM OF CANCER METASTASIS *

MONTROSE T. BURROWS, M.D.

ST. LOUIS

In previous articles [1] it has been shown that cancer may be only the result of a primary crowding of cells and a relative reduction of the blood supply to the mass. The change leading to cancer is not a primary change in the cell but in the organization of the tissue. The cancer cell grows and has the morphology peculiar to it on account of its immediate environment. These changes that the cells suffer in the cancerous tissue are reversible. These cells in an environment similar to that of the normal organism revert to nongrowing differentiated cells. They continue to grow in the cancer because the cancerous organization is able to destroy the surrounding normal tissue and blood vessels and reproduce the conditions necessary for the continuation of their growth.

It has been asked if cancer is due to such conditions how may the cancer cells break loose from the main tumor mass, migrate to distant parts, grow and form new tumors or metastases. The conception of cancer, as outlined above, has been the outcome of studies of the independent growth of normal body cells in the tissue culture. These studies have shown absolutely that growth, differentiation and function as they are seen in cancer and the normal organism are not determined by the cells, but are each simple responses of these cells to their immediate environment. The changes, such as growth, differentiation and function, which each cell suffers in normal development, are not determined by itself but by other more general formative forces in the organism. The cancer cell is not different from the normal cell, but merely a normal cell reacting to the immediate conditions of stagnation of environment and cell crowding.

The idea now more generally held assumes that the cancer cell is different from the normal cell. It is a cell equipped with a special mechanism for migrating about in the organism and one which can

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1. Burrows, M. T. South. M. J. **17**:233 (April) 1924; four articles in Proc. Soc. Exper. Biol. & Med. **21**:94, 1923; letter, J. A. M. A. **82**:323 (Jan. 26) 1924; Radiology **4**:407 (May) 1925. Burrows, M. T., and Johnson, C. S.: Action of Oils in Production of Tumors with Definition of Cause of Cancer, Arch. Int. Med. **36**:294 (Sept.) 1925.

grow independently under all conditions. This idea has not been built on careful analysis of the facts in the case, but is purely a theoretical notion built entirely on casual observations of the process.

The same idea of the independence of the cell has also permeated widely into a great deal of our modern biologic teaching. As Wilson [2] has clearly pointed out, however, many of the best biologists of the last and of the present century have been unable to find facts in support of this view. The picture of normal development of an animal or man is the action of some general formative force. The growth, differentiation and function of cells are secondary and wholly under its control.

As I have pointed out in previous articles there is no evidence that the cancer cell can grow independently in a tissue culture under other conditions than those necessary for an equally independent growth of normal cells.

When a fragment of embryonic mesenchyme 1 mm. in diameter is placed in a layer of blood plasma 0.5 mm. thick in a tissue culture, the cells in these fragments invade the medium, then grow and finally suffer a self digestion exactly as cancer cells suffer these changes in the body. As other studies have shown, these reactions are not reactions of the cell to specific substances in the plasma. They are the result of the removal of these cells from their normal circulation of blood in the organism to the stagnant culture medium that is well supplied with oxygen. The same reaction takes place readily when such a fragment is placed in a similar layer of pure isotonic sodium chlorid solution. These reactions which these cells suffer are the result of a gradual accumulation in this stagnant environment of a substance or substances, the archusia (S). The proof of this deduction has been made by extracting actively growing tissues of the body and the same tissues before and after they have been placed and allowed to remain in the stagnant medium of a tissue culture. The archusia is formed only in the presence of nutrient substances and oxygen. It is the energy not only for growth but also for all other manifestations of life of the cell. In low concentrations (S^1) the archusia has no effect. In medium concentrations (S^2) it causes the cells to migrate into a solid protein medium and toward larger droplets of fat. Smaller particles of proteins and small fat droplets are drawn in and stored in the cell. The connective tissue cells lay down intercellular substances under these conditions and other cells suffer their normal differentiation. In high concentrations (S^3) of the archusia these proteins and fats are digested, the extracellular materials suffer degeneration and the cells grow and divide by mitosis. In all higher concentrations (S^4) the cells themselves are digested.

2. Wilson, E. B.: The Cell in Development and Heredity, New York, 1925, p. 1030.

The changes, migration followed by growth and then self digestion, which the cells of a 1 mm. thick fragment of a cellular mesenchyme suffer when placed in a small amount of stagnant culture medium are only the result of a gradual accumulation of the archusia in these stagnant cultures. If one changes any of those conditions which are necessary for the accumulation of the archusia all of these manifested changes in the cells are slowed or inhibited completely. The concentration of the archusia is directly proportional to the number of cells acting per unit area, the nutrient substances and the oxygen present and inversely proportional to the amount of absorbing medium diluting it. As the concentration of the archusia is thus lowered the first of these processes to disappear is self digestion, then growth, and finally migration fails. If smaller fragments of the same tissue are placed in the same layer of medium the amount of archusia formed per unit time is less. With this decrease the appearance of the self digestion and growth is delayed and migration is slowed. As the fragments are made still smaller self digestion finally disappears except in the most central cells of the fragment. Then growth fails and, finally, when single cells are scattered in the medium migration also fails to appear unless archusia has been brought to the culture with them or extracted from other sources and added to the medium.

The actively growing embryonic tissues are rich in archusia. Mesenchyme cells isolated from them stretch out to take a spindle or irregular stellate shape in the medium and then become inactive. When archusia is extracted and added to the medium in small amounts these cells not only show these changes but also migration. If more archusia is added they grow and divide and show evidences of self digestion. Most adult tissues contain little or no archusia. Fibroblasts isolated from such fragments remain inactive in the medium.

By changing the thickness or the amount of medium about these fragments without changing their oxygen supply these reactions can be slowed or increased at will. The medium absorbs and dilutes the archusia as it is formed. These reactions take place, therefore, much more readily in thin layers of medium than in thicker ones. By washing these cultures with a stream of serum these reactions can also be slowed and inhibited completely. They begin again after the flow of serum is stopped and the archusia (S) can accumulate again about them.[3]

Oxygen is absolutely essential for this whole reaction. Recently Drew,[4] noting the self digestion in the centers of fragments of cancerous tissue in the body and in the centers of all fragments of tissues in the cultures about which growth takes place, thought this digestion

3. Burrows (Footnote 1, second reference).
4. Drew, A. H.: Brit. J. Exper. Path. **4**:46 (April) 1923.

an autolysis resulting from an absence of oxygen, as Champy [5] had originally described it. It is not an autolysis in any sense that we use the word autolysis at the present time. It is something that takes place in the presence of oxygen. It is the result of an excessive amount of the archusia about the cells. I have named it self digestion, therefore, to distinguish it from autolysis, which is the result of the absence of oxygen. Oxygen diffuses into clots of plasma no more than from 0.5 to 0.7 mm. and no more than 1 mm. into most tissue fragments. If one increases the thickness of the fragment or the layer of medium above these limits, the migration, the normal growth of the cells, and their self digestion is immediately inhibited. A true autolysis proceeds in the centers of the fragments and in all parts of it which lie beyond the limits of the diffusing oxygen. The toxic products diffusing from these autolyzing cells inhibit the reaction of cells lying in the zone of oxygen diffusion.

Warburg [6] also has recently noted that less oxygen is absorbed and carbon dioxid given off by cancerous than by normal tissue. At the same time he finds an excessive breaking up of sugar to lactic acid in the cancerous tissue. He assumes, therefore, from these observations that cancer is the result of a reduced oxidation and that its energy for growth is derived from the fermentation of sugar. Smith [7] in this country has advocated this view. As pointed out in the foregoing, an excessive amount of archusia such as is found in cancerous tissue leads not only to a splitting of sugar but to a splitting of the entire protoplasm of the cell. The archusia is formed by the oxidation of foods in the cell. It is well known from the "Law of Mass Action" that the velocity of such a reaction leading to the oxidation of food with the formation of the archusia is directly proportional to the concentration of the reacting substances (food and oxygen, in this case) and inversely proportional to the concentration of any one or all of the substances formed by the reaction. Carbon dioxid and the archusia are two of the products formed in this reaction. The carbon dioxid escapes, the archusia remains. As the archusia concentrates more and more this reaction must become slower and slower in the same proportion. Such an accumulation is found in cancerous and all growing and highly functioning tissues. The archusia escapes from the cells in the normal organism by way of the blood stream. The amount of oxygen used by the cells of the normal organism must be much higher, therefore, when these cells are isolated than that used by a cancerous tissue. I have found in the study of the growth, migration and function of normal embryonic cells in the cultures that oxygen is essential only for

5. Champy, C. L.: Rev. gén. d. Sc. **24**: 790, 1913.
6. Warburg, Otto: J. Cancer Research **9**:148 (March) 1925.
7. Smith, E.: Science **61**:595, 1925.

the formation of the archusia. In the presence of the archusia all the other reactions essential for these processes proceed without oxygen.[8] The archusia is to the cell what the heat is to the steam engine. Oxygen is necessary for the steam engine only for the liberation of heat. The other reactions of the engine then proceed without oxygen.

Recently Barta,[9] working in my laboratory and in other laboratories at Washington University School of Medicine, has shown that reduced oxidation does not stimulate growth in tissue cells but leads to the transformation of the cells into recticular and giant cells and to autolysis. These changes can be prevented by adding either oxygen to the cultures or archusia extracted from other sources.

Warburg attempts to strengthen his argument in favor of the view that the energy for growth in cancer is derived from the fermentation of sugar by showing that Meyerhoff [10] had come to the same conclusion in regard to muscular contraction. As must be pointed out here, the facts brought forward by these authors in support of such a view are too few to warrant the conclusion. The facts I have enumerated in the foregoing disprove it. These fermentation processes which they describe are only secondary processes in the synthesis of protoplasm and the result of a high concentration of the archusia.

The same conditions that I have outlined above as necessary for the growth of normal embryonic mesenchyme cells are also necessary for the growth of other cells of the embryo, cells of adult animals and the cancer cells. The cells of these various tissues vary in their reactions only in proportion to their original archusia (S) content in the body. Cancerous and embryonic tissues are rich in this substance while adult tissues contain only traces of it. This difference in the amount of archusia in these tissues is not related to any peculiarity of the cells, but to the blood supply and to other conditions regulating its formation and escape from about the cells. The cells of the malignant tumors react in the cultures in proportion to their original growth rate in the body. The other difference between the cancer cells and those of the young embryo when placed in the cultures is that the cancerous tissues degenerate more quickly than the embryonal cells. I had wondered whether this difference might not be due to a greater quantity of nutrient substances in the embryonic tissues than in the cancers. In recent experiments in which these various tissues were fed to rats, we have found a greater quantity of vitamin A in the embryonic than in the tumor fragments.[11]

8. Burrows, M. T.: Proc. Soc. Exper. Biol. & Med. **18**:133, 1921.

9. Barta, E.: Unpublished data.

10. Myerhoff, O.: Chemical Dynamics of Life Phenomena, Philadelphia, 1924.

11. Burrows, M. T., and Jorstad, L. H.: On the Source of Vitamin B in Nature, Am. J. Physiol., to be published.

Adult cells react the same but always after a longer latent period. The cells of adult connective tissue are widely separated by intercellular substances. They are like the fragments of the cellular tumors and of the embryo which have been teased apart. The longer latent period has been shown to be due to the small quantity of archusia which they contain in the body and to the presence of growth inhibiting substance (ergusia or vitamin A) in them. The actively growing embryonic cells and cancer are already rich in archusia when transplanted. The archusia does not reach S_2 concentration in the normal adult tissues, except in fragments of the skin, hair, bone marrow and the cells from other actively functioning and growing centers, until these fragments have remained for a time in the stagnant cultures. If these fragments are left for a long time in the stagnant culture medium and are then transplanted to fresh plasma they react after a short latent period as the cells of the cancers and the embryos.[12] The latent period for the growth of the cells in fragments of actively growing cancer and embryos is evidently only the result of a temporary dilution of the archusia by the plasma of the culture which is free from it. The longer latent period of the inactively growing cells of the adult is the period necessary for the archusia to accumulate in the fragments suffering stagnation and for the plasma to remove the growth inhibiting substance from them.

When the archusia is extracted from other sources and added to the plasma of a culture it stimulates cells to grow. The embryonic and the cancer cells react more quickly to the archusia than the normal adult cells. The normal adult cells in their differentiation or long sojourn in an environment poor in archusia had undergone changes that inhibit their reaction. These changes are not irreversible. After these cells have remained for a time in the presence of the archusia they grow. If they are then removed in this growing state to fresh medium containing archusia they react quickly to it as the growing embryonic and cancer cells. The skin epithelium of the adult frog is a thin layer of cells. The cells are continuously growing in it. The cells have ceased to grow in the underlying connective tissue layer of the skin of these frogs. The epithelial cells show activity within from one to two hours after a fragment of skin is transplanted to a layer of plasma. The connective tissue cells under the same conditions will not react until after twenty-four, ninety-six or more hours. This activity of the epithelial cells can be inhibited entirely by stripping the epithelial layer from the underlying connective tissue and laying it in the plasma. The plasma in contact with both sides of the layer absorbs the archusia in it as fast as it is formed. The archusia cannot reach a concentration

12. Lambert, R. A.: J. Exper. Med. **17**:499, 1913.

in the layer sufficient to induce activity in the cells. If, on the other hand, one rolls such a layer into a compact mass the cells show migration.

From these observations I was forced to believe that body cells are not fundamentally different from unicellular life in general in nature. It is in the stagnant pool and not in the running stream that such life abounds. Cellular growth in the animal body is most active in the early periods of development. It wanes and ceases as the blood vascular system develops and the cells become separated by this active blood flow except in certain regions, skin epithelium, hair, nails, sex glands and bone marrow, in wounds, tissues suffering hypertrophy and hyperplasia and in cancer.

In previous articles [13] it has been shown that growth in each of these places or under each of these conditions is associated with a stagnant circulation and an overcrowding of cells. This stagnation and overcrowding is greatest in cancer.

These facts had led me to believe that cancer may be nothing more than the result of a local crowding of cells and a relative reduction in the blood supply to the mass. In proof of such a conception it has been possible to show:

1. The various substances and conditions known to be able to induce cancer, such as coal tar, other lipoid solvents, roentgen rays, radium, animal parasites, bacteria, chronic inflammation, congenital defects and anomalies, act only to produce such a tissue organization. We have shown that coal tar [14] and other lipoid solvents [15] have no stimulating value for the cells. Drops of coal tar and many other oils placed in the tissues cause the cells to degenerate. In so doing they also attract cells to them from wide areas of the tissue about them. These drops become encapsulated by a dense mass of cells. This action of coal tar is always limited. While many of the cells degenerate in this capsule others remain intact and recuperate readily after the action of the tar has ceased. If sufficient cells have accumulated an active growth of them intervenes in this stagnant environment and cancer develops. If fewer cells are accumulated the connective tissue cells lay down intercellular substances [3] and the epithelial cells proliferate for a time but eventually the whole reverts to a hyaline scar.[16]

Animal parasites and bacteria produce this dense mass of cells largely free from blood vessels by stimulating directly through their own archusia an active local proliferation of cells without the formation

13. Burrows, M. T.: J. M. Res. **44**:643 (Sept.) 1924; Footnote 1, first and fifth references.

14. Jorstad, L. H.: J. Cancer Res. **9**:232 (June) 1925.

15. Burrows (Footnote 1, fifth reference).

16. Burrows, M. T., and Johnston, C. G.: J. Exper. Med. **42**:215 (Aug.) 1925.

of blood vessels.[15] Roentgen rays and radium[17] disturb the blood vascular supply as well as increase the metabolism or the production of archusia in the cells exposed.

2. In other experiments[18] it has been shown that any dense mass of cells not only grows readily but also destroys any neighboring less dense mass of cells as cancer destroys the normal tissues about it. In this destruction the blood vessels as well as other tissues suffer. Thus any dense mass of cells once established in the organism must continue to grow indefinitely in that it can reproduce its own stagnant organization through the destruction of normal tissues and blood vessels about and within it.

3. The third proof of this conception is found in the close similarity in the growth of cells in a tissue culture to that in cancer. As is well known and as has been pointed out in previous articles the cells in a tissue culture do not grow to form organ structure but invade the medium and grow in it as cancer invades the organism. The conditions that allow these cells to grow independently in this manner in the cultures are stagnation and cell crowding, as has been shown in previous articles and outlined in the foregoing.

In this paper it became of interest to see if this analogy could be carried further and whether cancer metastases can be explained on the same basis. The problem of metastasis is the problem of the mechanism of the migration of these cells and their ability to grow and form new tumors by this growth in parts removed from the original tumor.

One of the strongest arguments that has been raised in support of the view that the cancer cell is different from the normal cell is that it can invade the tissue, migrate to distant parts and form metastatic tumors. There is no evidence that under normal conditions the epithelial or other of the fixed tissue cells can perform these acts. The question therefore arose, Can these acts be resolved to the same conditions of overcrowding and stagnation, or are they something peculiar to a specifically differentiated cancer cell or to some parasite or other agent, as certain English and American authors are now attempting to prove?[19]

The earlier work on the tissue culture had already shown that the mechanism for migration of normal cells that are crowded in densely cellular fragments in the tissue culture is not the same as that of the same cells when they are transplanted in smaller fragments. Harrison,[20]

17. Burrows, M. T.; Jorstad, L. H.; Lunsford, C. J., and Ernst, E. C.: Paper read before the Internat. Congr. Radiology, London, July, 1925.

18. Burrows (Footnote 13, first reference).

19. Nuzum, J. W.: Surg., Gynec. & Obst. **4**:343 (March) 1925. Ochsner, A. J.: Ibid. **40**:336 (March) 1925. Gye, W. E.: Lancet **2**:109 (July 18) 1925. Barnard, J. E.: Lancet **2**:117 (July 18) 1925.

20. Harrison, R. G.: J. Exper. Zool. **9**:787, 1910.

in his earlier attempts to observe a growth of nerve fibers from fragments of the neural tube of frog embryos, placed these fragments of the nervous system in hanging drops of serum. No growth was observed. Success was attained only when he placed the fragments in drops of lymph which clotted to form a solid medium. It was into this solid medium that the nerve fibers grew and the cells migrated. He notes that the nerve fibers grew out and the cells migrated always in contact with the fibrin fibrilli of the clotted lymph. Harrison therefore concludes that these cells are stereotropic and that solid support is a necessary factor for their migration and growth.

In developing a more general method for culturing cells of higher animals, I used blood plasma as medium. The plasma clots to a solid gel when the tissue cells are added to it. Into this medium it has now been found that all types of cells of adult and embryo may migrate readily.

In 1911, M. R. and W. H. Lewis [21] observed an active migration and growth of cells from fragments of tissue of chick embryos into hanging layers of simple physiologic sodium chlorid solution and other liquid mediums and serums.

Harrison [22] repeated these experiments of the Lewises to find that the cells did not migrate directly into hanging drops of these liquid mediums, but they moved always along the cover glass or lower free surface of such hanging drops. I also studied these cultures of the Lewises. I found that only the cells from actively growing and densely cellular fragments of tissue can migrate and grow in this medium.[23] The cells from similar fragments of older embryos and adults cannot migrate unless these cells have been previously brought to an actively growing state by replanting fragments of them in drops of plasma.

It was also noticed that when one reduces the size of the densely cellular fragments of the younger embryos and of cancer and separates the cells slightly within them that these cells also cannot migrate nor grow in a liquid medium. In plasma the cells of the same small fragments migrate readily but they do not grow. In comparing the behavior of the same large and small fragments in both a liquid medium and plasma, it was interesting to note than when one reduces the size of a fragment of mesenchyme so that its cells fail to grow in equally thin layers of plasma that they also simultaneously fail to migrate along the surface of a liquid. When the fragment is large enough for the cells to grow readily in the plasma they are then able to migrate and grow along the surface of a liquid medium.

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21. Lewis, M. R., and Lewis, W. H.: Anat. Record **5**:277, 1911.

22. Harrison, R. G.: Science **34**:279, 1911.

23. Burrows, M. T.: Anat. Record, 1917, p. 335; J. Cancer Research **6**:131 (April) 1921.

These facts had led me to study more carefully the migration of mesenchyme and epithelial cells from the large and the small fragments into plasma clots. From the smaller fragments the cells migrate directly into the plasma clot. The clot contracts ahead of them and becomes transformed into fibrin. The cells cling tightly to these fibrin fibrils. This migration is most rapid at first. It slows gradually as the cells become more and more separated. Eventually these cells come to rest and lie intact but inactive for an indefinite period. During this migration they have shown no growth but have decreased in size except as they have suffered swelling from the fat droplets they have accumulated in their cytoplasm.

About the larger densely cellular fragments the picture is different. The first cells to appear enter the clot. Most of these then soon leave the clot to move on one or the other or both of its surfaces. In the clot the mesenchyme cells have a slender spindle shape. Their boundaries are sharply defined. Their nuclei are seen with difficulty except when they are stained and their cytoplasm contains fat droplets. On the surface of the medium they often contain no fat. They are flattened to spindle or polygonal shaped plates. Their nuclei become visible, occupying their entire vertical axis, and their edges becomes indistinct. These cells in this position grow rapidly, divide by mitosis, show an early vacuolization of their cytoplasm and later suffer a self digestion (Fig. 1).

At an earlier time I had already studied the mechanism of migration of these cells from these two sized fragments. The results of this work are reported in another paper.[24] Body cells, unlike ameba and many unicellular organisms, migrate only in straight lines away from a fragment and other cells. In this migration they may or may not show any ameboid movements. From the smaller fragment the migration of these cells is entirely the result of their liberating a soaplike substance that is absorbed only by proteins, fats and other similar substances. It is insoluble in water and does not decrease the surface tension of water. This substance liberated by the fixed tissue cells also coagulates fibrinogen to fibrin. It is readily absorbed by the fibrin and decreases the surface tension of the cell in contact with the fibrin. The cell is thus stuck to the fibrin and moves in the line of the diffusion of this soaplike substance. This soaplike substance I have called the ergusia or the laboring substance of the cell. It is also readily absorbed by fats. Smaller particles of proteins and small fat droplets are drawn into the cell by it while the cell moves into protein

24. Burrows, M. T.: Energy Production and Transformation in Protoplasm as Seen Through a Study of the Mechanism of Migration and Growth of Body Cells, to be published in Am. J. Anat., 1925.

clots which are attached to rigid bodies without and toward and against large fat droplets having a greater inertia than themselves.

The ergusia is not liberated by the cell under all conditions, but only when the archusia reaches an S_2 concentration. The effects of the liberation of the ergusia are seen about the smaller fragments, but fail the cells completely isolated in a clot unless the archusia (S) is added from other sources.

Under the influence of a greater crowding of the cells and the S_3 concentration of the archusia which results, the whole picture of activity in the cell changes. It digests the proteins and fats of its environment and absorbs water rapidly. Under the influence of an S_4 concentration the cell is digested.

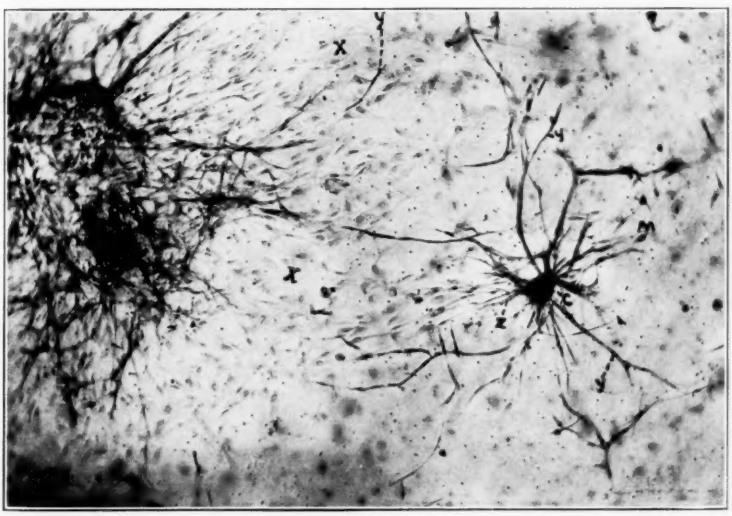

Fig. 1.—Culture of fragments and isolated cells of heart of 10 day old chick embryo in medium of plasma prepared from blood of adult chicken, fifteen hours after the chicken had eaten; three fragments and a few isolated cells are shown. The culture was 48 hours old when it was fixed in formaldehyd and stained with Delfield's hematoxylin. The plasma layer was originally 0.3 mm. thick; the larger fragments were originally 0.3 mm., and the smaller one was a little more than 0.1 mm. The larger fragments, *A* and *B*, show the typical reaction of all the larger cellular fragments of tissue in the cultures. The cells in the center of these fragments have suffered a self digestion and the liquid liberated in this self digestion has spread over the surface of the plasma layer. The border cells of each of these fragments have moved out and dispersed into the clot and into this surface film; in the film they are flattened and stain less sharply, *X;* in the plasma they are slender spindles and more compact, *Y*. No surface film has formed about the smaller fragments, *C;* its cells are moving into the clot; the surface film from the larger fragments passes under this smaller one. Where the cells from the smaller fragment have become caught in this film they have flattened, *Z*, and one of these cells in this film is dividing, *M*.

In this digestion we noted that a liquid substance is liberated. This liquid is also insoluble in water but, quite different from the ergusia, it decreases the surface tension of water. It flows readily over the surface of salt solution or plasma. In the cultures in which salt solution and liquids had been used as medium the cells had not migrated into the liquid medium nor in contact with it, but into this liquid film which had spread from the fragments. The cells in the centers of the larger fragments had suffered an early self digestion.[25] These films are only the result of an overcrowding of the cells in the centers of the fragment or an excessive accumulation of the archusia (S) in this region. In these cultures all of the cells which migrate do not reach the surface films. A few of them remain in the plasma clot (Fig. 1). These cells as they move farther out finally come to rest as the cells migrating from the smaller fragments. The cells which grow at a distance from the fragments in the cultures are only those cells which are bathed with an excessive amount of archusia carried in the special surface films liberated by the cells digesting in the central parts of the fragment. The cells which had migrated into the clot are not different from those on the surface. If one removes them to the surface film they flatten as the other cells flatten, grow, divide by mitosis and later suffer the self digestion.

These conditions, which are necessary for the growth of the normal cells, are also absolutely essential for the growth of the cancer cells in vitro. When one reduces the size of the fragments of cancer and separates the cells in them so that the cells in the center of these fragments fail to suffer self digestion and liberate the substances that form the films, these cells cannot migrate along the surface of a liquid. They migrate into a plasma clot but as they separate from each other and their archusia has become diluted about them they come to rest exactly as the normal cells come to rest under these conditions (Fig. 2).

In the normal adult organism the concentration of the archusia as shown by extractions does not exceed a concentration of S^2 except in the few growing areas, bone marrow, sex glands, skin, nails and hair. In these regions it is barely S^3. No self digestion of cells is seen under normal conditions except in certain periods of early embryonic life. The pronephros and metanephros suffer such a digestion. In cancer conditions are different. The archusia is always S^3 and S^4 in this tissue. This high concentration of the archusia is due to the fact that the cells are overcrowded in this region and their circulation is greatly impaired. The central parts of the cancer suffer the same self digestion as that seen in the larger compact fragments of the culture.

In the plasma clot the cells from the smaller fragments can migrate only until the clot becomes saturated with the ergusia. The intercel-

25. Burrows, M. T.: Burn, J. E., and Zusuki, Y.: J. Urology **1**:3 (Feb.) 1917.

Fig. 2.—Culture of fragment of Rous chicken sarcoma in plasma prepared from blood of normal adult chicken; the culture was fixed in formaldehyd and stained with Delfield's hematoxylin when 72 hours old. The picture shows one edge of the fragment. The fragment was originally 1 mm. in diameter and the plasma layer 0.5 mm. in thickness. The central cells of the fragment have undergone a self digestion and liquefaction. A film of fluid has moved out over the lower surface of the clot of plasma. The tumor was originally a round cell type. The border cells of the fragment have moved into the clot and into the film of fluid over the lower surface of the medium; in the clot they have reverted to a spindle cell type and have ceased to grow; in the surface film they have remained as round cells; those near the fragment are degenerating; those farther out are growing. As many as five mitoses may be seen in a single low power field in this region. Even the cells of this tumor of Rous, which contains special stimulating substances unknown to human cancers and to other cancers of chickens and of other animals, respond to the same conditions and in the same manner as normal cells.

lular substances of the body are so saturated. Into a wound fresh plasma exudate has been exuded. The cells migrate readily into this exudate. They grow in this stagnant area until their circulation has been reestablished.[13]

The question arose, Are metastases the result of the same conditions? In the cultures it has been noted that this fluid liberated in the centers of the fragment spreads as readily over the surface of a plasma clot as over the surface of salt solution. When it spreads over the surface of a drop of salt solution it makes this surface leathery so that it cannot be made to run easily when the slide is tipped on which it is lying. It is a fluid, therefore, which can decrease the surface tension of water much more than any fluid known to exist in the normal organism. It should therefore be able to flow readily over the surfaces covered by differentiated cells of the body. In proof for this last possibility it was found that it can flow readily over the surface of a plasma clot filled with ground normal tissues and over neighboring fragments of normal tissues placed in the culture medium. Cells coming from these normal fragments and caught in these films eventually grow and divide by mitosis (Fig. 1).

In the body metastasis of cancer takes place along the surface of the lymphatics, blood vessels and other tissue surfaces or by way of the blood stream to distant organs. Their chief course is always, however, along the lines of surface drainage from the original tumor mass.

It therefore became of interest to see if these streams of fluid preceded the spread of the cancer cells in the organism. One of the chief means of testing for the existence of this fluid is its ability to stimulate growth in normal cells. I have looked for the existence of this growth stimulating fluid in the blood stream of patients with generalized and extensive metastases and in the lymph glands and other tissues about cancers previous to the spread of their metastases.

CHANGES IN TISSUES ABOUT DEVELOPING CANCERS

During recent years a large number of patients with early cancer of the lip, breast, other areas of the skin, genitals and internal organs have entered the clinic. It has been the experience of the clinic that simple removal of these tumors, except certain of the basal cell cancers of the face and of the extremities, does not effect a cure. The glands draining the cancerous regions must also be removed. This has given us a wealth of material to study the early changes in the lymph gland and other tissues about these tumors. I have collected the specimens from 400 of these tumors. In this group there are 360 carcinomas, thirty-two sarcomas and eight melanomas. Most of these tumors were from 2 to 6 months old. Others had endured for no more than a month before operation.

In every case the picture was the same. There is marked hyperplasia of the endothelial cells lining the lymph vessels draining the cancer and similar extensive hyperplasia of the lymph glands into which these vessels drain. In the lymph glands this hyperplasia begins along the periphery or the entrance of the afferent vessels. It involves not only the germinal centers but also the whole of the gland. The endothelial cells lining these afferent vessels have proliferated. They are no longer a thin layer of flattened cells, but appear now as a closely set layer of cuboidal cells, one to several in thickness. The same proliferation is seen in the cells lining the sinuses of the gland. In

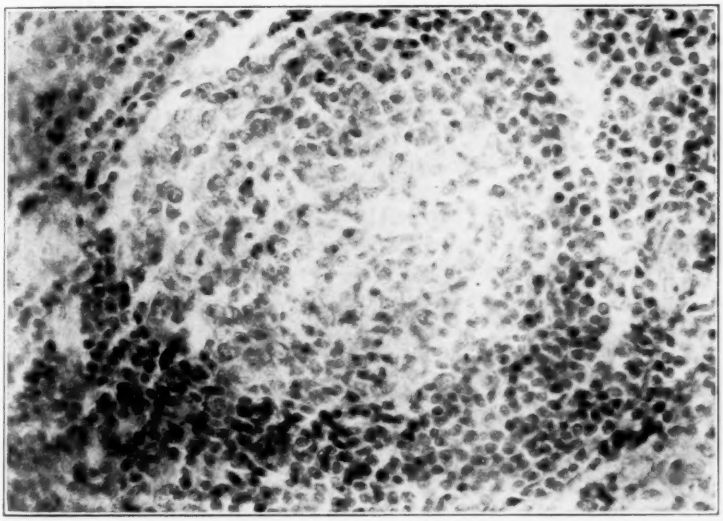

Fig. 3.—Section of gland of neck draining material from a cancer of the jaw, under moderately high power; the picture includes a small follicle showing mitoses; there are mitoses also in the cells of the surrounding glandular tissue.

many places this proliferation has proceeded until the whole sinus is filled with these cells. The germinal centers have increased greatly in size. In the earlier stages they appear as a dense mass of cells. Later the centers of these masses degenerate and clear; this makes them stand out prominently in the stained specimen. Mitotic figures are seen in all parts of the gland. They are especially prominent in the germinal centers (Fig. 3). In this region the cells degenerating show exactly the same appearance as the normal cells growing, dividing and degenerating about any densely cellular fragment of normal tissue placed in a tissue culture.

This hyperplasia is seen in the glands draining every cancer. It is as common in the glands draining melanomatous and sarcomatous tis-

sue as in those draining fluid from a carcinomatous tissue. In many of the older subjects these glands had atrophied and become replaced by a large mass of fat. This fat fills their hila and central parts. In these cases the cells proliferate first along the circumference and gradually remove the fat as they grow and increase in number.

The picture of hyperplasia in the lymph glands of cancer that I have given is not new. It has been observed and described by previous authors.[26] Its significance has become possible of understanding, however, only in the light of the studies of the conditions regulating the growth of normal cells as protrayed by the tissue culture.

It is into these hyperplastic glands that the cancer cells invade and grow to form new tumors. The growing lymphoid cells are then rapidly destroyed by the loss of their substance to the cancer cells. The cancer cells predominate in most of these cases merely because they have become adapted to respond more quickly to these stimulating substances than the other normal cells. This need not, however, be the case. There are numerous instances in the literature in which the normal cells have undergone malignant transformations at a distance from the cancers. L. Loeb and also Lewin [27] report cases in which the skin epithelium of a normal rat underwent malignant transformation in the neighborhood of a transplanted cancer. Malignant transformation of the stroma of both transplanted and human cancers is well known. I succeeded in inducing a cancer in the skin of a rat by reducing the circulation of the skin by pressure and injecting fragments of embryo rat plus a Berkefeldt filtrate of a Jensen sarcoma. The Berkefeldt filtrate of the Jensen sarcoma of the rat unlike that of the Rous chicken sarcoma will not induce tumor when injected into normal tissue.[28]

It is easy to induce a growth of the cells in a fragment of normal tissue too small for them to grow when it is isolated in a drop of plasma by placing it near a larger fragment even when the cells of the larger fragment are not able to grow. The archusia from the larger fragment uniting with that of the smaller fragments leads to a digestion of the cells in the center of the smaller fragment, a surface film, an invasion of the medium, and a growth of the border cells of the smaller fragment.

CHANGES IN THE BLOOD OF CANCER PATIENTS

Several authors have noticed an alkalosis of the blood of cancer patients. The significance of this had never been investigated. It was interesting, however, in going over the literature on this subject to notice that although the alkalosis was often considerable that these patients

26. Ewing, James: Neoplastic Diseases, Ed. 2, Philadelphia, 1922, p. 78.

27. Loeb, L., and Lewin, cited by Burrows, M. T.: J. Missouri M. A. **20**:145, 1923.

28. Burrows (Footnote 27).

never showed any evidence of tetany. The question that arose was, Is this alkalosis due to a change in the carbon dioxid-bicarbonate ratio, or to the addition to the blood of other substances? I asked Dr. Chambers [29] to investigate this question. Using the indicator method on dialysates of the blood of these patients he found no evident alkalosis in the early stages of cancer. As the cancer advanced and metastasis appeared the alkalosis appeared and became more and more pronounced as the metastasis spread to distant parts. According to his results the dialysate of normal persons has a p_H of 7.3 while in many cases of cancer with liver metastasis it reached a value of 7.6. There was no difference apparently between carcinomas, melanomas and sarcomas in this regard.

Having established this fact, Chambers then studied the carbon dioxid-bicarbonate ratio in these cases. He found it always normal. Evidence of an alkalosis was found only in the dialysate. It was not the result of changes in the carbon dioxid-bicarbonate ratio but evidently the result of the addition of some acid protein substance to the blood which could not pass through the celloidin sacs with the hydroxyl ions with which it had combined.

OTHER STUDIES ON THE BLOOD OF CANCER PATIENTS

In recent years many students of the tissue culture have described stimulating substances in the blood of cancer patients. In most instances this work has not, however, been reliable because no controls were made of other conditions that might change the growth of cells in a normal plasma. Our results of these studies have been more or less irregular. In general it has been interesting to note that the blood plasma of patients with advanced cancer stimulates the cells more than normal bloods.

One difficulty that arises in making these tests is that fat in the blood inhibits the growth of cells in it. The cancer patients suffering anemia have a higher fat content in their blood than normal patients. This fat can be decreased by starving. I have attempted through short periods of starvation to equalize the fat in the blood of animals with cancer with that of normal animals. In such experiments a definite stimulating value has always been found in the blood of cancer animals (rats). When the blood is taken without respect to eating and fat content the results have always been irregular. This stimulating value in the blood plasma of the cancer animals is greater in the blood from those animals in which the cancer is metastasizing.

The experiments on man have been equally difficult. In these studies I compared the growth of embryonic chick tissue, human can-

29. Chambers, W. H.: J. Biol. Chem. **55**:229 (Feb.) 1923. Chambers, W. H., and Kleinschmidt, R. E.: Ibid. **55**:257 (Feb.) 1923.

cerous tissues and normal tissues taken from arteries removed at hernia operations on children and young men. These tissues were cultivated in bloods of normal men under normal conditions and after they had starved themselves for from twelve to twenty-four hours, patients with acute infections (pneumonia and typhoid fever), alcoholic patients recovering from a period of drunkenness, patients with chronic tuberculosis and cancer patients. Starvation of moderate degree makes the blood plasma a much more efficient medium. The plasma prepared from the blood of the acutely ill patient and the alcoholic patient is toxic. The blood of cancer patients is always a good medium. In summing up our results it was found to be in general always better than the others.

As must be pointed out here, the process of growth is not merely the result of the action of the stimulus, the archusia, but depends also on the presence of other food substances in the medium. The stimulus acts only to change the protoplasm so that it attracts the necessary substances for growth into the cell, the proteins, the fat, the carbohydrates, the water and the salt. It then induces chemical changes between them and protoplasmic synthesis. Each of the various cells that compose the body, the liver cells, the muscle cells, the brain cells, differ from each other in their chemical and physical make-up. For them to grow they also must each demand more or less specific substances and other specific conditions.

For metastasis to localize in distant organs or tissues these points of localization must not only be sites where the circulating stimulus can collect, but they must also contain an ample collection of other nutrient substances for the growth of the cells.

It is not surprising, therefore, that in generalized metastases we find certain cells tending to metastasize only into certain regions and that we find certain organs immune from such metastasis in many persons.

COMMENT AND SUMMARY

From the foregoing observations it became evident that metastases in cancer are not the result of a simple migration of cancer cells from the cancer to distant organs. Metastases are primarily the result of the spread of a liquid substance from the main tumor mass. This substance spreads over surfaces. It is liberated through a digestion of cells in the center of the mass of cancerous tissue. This digestion is not an autolysis resulting from the absence of oxygen, but the result of an excess of the growth stimulating substance, a product of the cell's oxidation. This fluid is rich in growth stimulating substance. This fluid stimulates not only the cancer cells to grow but also the normal cells. The cancer cells already adapted to it respond more quickly. In their growth they then remove the nutrition and necessary substances from the other cells and destroy them.

This type of reaction may not always occur. As is well known the normal tissue may undergo malignant transformation. Such has been seen frequently in transplanted cancers of animals. These transformations are the result of a sufficiently long action of this fluid.

While these observations are interesting in throwing light on the nature of the mechanism of cancer metastases their greater importance is the more absolute proof they give for the cause of cancer.

In 1920 when we began to study the cause of cancer intensively at the Barnard Hospital, it had been shown that cancer can be induced by any one of a number of substances and conditions, such as coal tar, other lipoid solvents, bacteria, animal parasites, roentgen rays, radium, arsenic and other substances. In man as well as in animals it is a disease of old age and may occur not only through the action of any one of the substances mentioned in the foregoing but also in congenital tumor and defects, in old chronic inflammatory areas, in tissues suffering atrophy from old age and tissues forced to atrophy from various external factors, such as exposure to sun and weather.

While animal experiments had shown definitely that any of the substances or conditions mentioned in the foregoing can induce cancer the same experiments had also shown that the same substances are not concerned or necessary for the subsequent growth of this disease. Cancer once induced by coal tar grows indefinitely to the destruction of the host without any further additions of this substance. Many cancers induced by coal tar have been transplanted to other animals and have continued to grow as actively as ever long after the tar has disappeared.

It became evident from these observations that cancer is not the result of any specific substances or group of substances. It is the result of some primary change either in the cell or the tissue which may be induced by any one of a number of widely different substances and conditions.

In view of the fact that no one had been able to show that the cancer cell is different from any other cell and that cells can grow in a tissue culture in a medium of the blood plasma of the body only when they are crowded in considerable numbers into a small amount of this medium, which is well supplied with oxygen, the question arose, May not cancer be only the result of cell crowding and stagnation in the body?

To assume that cancer is the result of irritation and then the invasion of a parasite was not possible in the light of any known facts. It therefore became of interest to study the action of the various substances in inducing cancer. It was found that each acts only to induce the formation of a dense stagnant mass of cells having a reduced blood supply. Drops of coal tar produce such a tissue organization by attracting the fixed tissue cells to them and crowding them about their peri-

pheries. Bacteria and animal parasites when introduced into the tissues stimulate the cells to proliferate without the formation of blood vessels and intercellular substances. Roentgen rays decrease the blood supply and also stimulate the cells.

The question that concerned us, therefore, was whether metastasis as well as the independent growth of cells can be explained by the same cell crowding and stagnation. In previous work it has been noted that cells of large, densely cellular fragments can migrate along the surface of a medium independent of any specific absorbing substances in the medium. They accomplish this by the fact that a liquid is liberated from the centers of these larger fragments. This liquid can flow over any water surface. The cells move into it. In this article it has been possible to show that such a fluid precedes the spread of cancer cells and metastases in the organism. It has thus been possible to give practically absolute proof for the foregoing deductions of the nature of cancer by showing that the whole phenomenon can be reproduced by simply cutting down the blood supply to a cellular tissue and allowing the cells time to revert from the differentiated to the growing state.

CHRONIC AND ACUTE ARTERITIS OF THE PULMONARY ARTERY AND OF THE PATENT DUCTUS ARTERIOSUS *

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MILWAUKEE

The association of a congenital cardiac anomaly and an inflammatory process of the heart valves is well known. A congenital anomaly of the heart with inflammation of the pulmonary artery with or without valvular endocarditis, however, is unusual. The object of this article is to record an instance of pulmonary arteritis with thrombotic occlusion of the pulmonary bulb and the patent ductus arteriosus in a child aged 8 years. This particular association of arteritis with a congenital cardiac anomaly is unusual, as shown in the following survey. The accompanying table includes nineteen cases of patent ductus arteriosus with arteritis of the pulmonary artery. In only three of these (Krzyszkowski,[1] 1902; Hamilton and Abbott,[2] 1914; Schlaepfer, 1926) were the heart valves intact and the inflammatory process restricted to the pulmonary artery and the ductus arteriosus. In the remaining sixteen cases a valvular endocarditis was present in addition to the inflammatory lesion encountered in the pulmonary artery and in the patent ductus arteriosus.

Four observations not included in the foregoing, published by Rauchfuss,[3] on infants from 1 to 2½ weeks of age must be mentioned. The author correlated the thrombosis, which in these cases was confined to the patent ductus arteriosus, with "puriform thrombi" found in three instances in the vessels of the umbilical cord. The fact that a thrombus was present in the ductus arteriosus together with a blood stream infection made these observations seem worth recording.

REPORT OF CASE

A. F., a white boy, aged 8 years, was sent to the outpatient department of the New Haven Hospital in June, 1924, by the school nurse for a "weak heart." The family history was unimportant.

It is noteworthy that the patient never had rheumatism; whooping cough and measles were the only diseases of early infancy. Until June, 1924, neither

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1. Krzyszkowski, J.: Aneurysma des Stammes der Pulmonalarterie und multiple Aneurysmen ihrer Verästelungen bei Persistenz des Ductus Botalli, Wien. klin. Wchnschr. **4**:92, 1902.

2. Hamilton, W. F., and Abbott, Maude E.: Patent Ductus Arteriosus with Acute Infective Pulmonary Endocarditis, Tr. A. Am. Phys. **29**:294, 1914.

3. Rauchfuss, C.: Ueber Thrombose des Ductus arteriosus, Virchows Arch. f. path. Anat. **17**:376, 1859.

family nor patient were aware of any abnormality. At the dispensary, a diagnosis of patent ductus arteriosus was made based on the following findings:

The left border of the heart was found 0.5 cm. within the nipple line and an impulse was felt in the fifth intercostal space. A suggestion of a thrill in the pulmonic area was noted. The sounds were of good quality. A loud rumbling murmur in the pulmonic area replaced entirely the first pulmonic sound. The second sound was accentuated.

The child was kept under observation in the outpatient department but no untoward symptom arose until December, 1924, i. e., six weeks before admission to the hospital, when examination of the ears revealed dulness and injection of both ear-drums. Two weeks later the boy developed a "cold"; the ears discharged, fever developed, the child became bedridden and complained of pains in several joints.

He entered the New Haven Hospital, Jan. 22, 1925. Physical examination now revealed marked dyspnea and inspiratory retraction over the supraclavicular fossa and below the xiphoid process, a perforated right ear-drum, a slight enlargement of the heart toward the left at the apex, a soft systolic and a faint diastolic murmur over the whole precordium, and a continuous murmur at the base. The temperature was 40.2 C., the pulse rate 120, and the respiration rate 54 per minute. The red blood count was 3,632,000 with 80 per cent hemoglobin; the white cell count, 22,400 with 83 per cent polymorphonuclear leukocytes; there were numerous colonies of *Streptococcus viridans* from the blood.

The illness progressed rapidly. The temperature became septic in type. Repeated cultures from the blood revealed numerous colonies of *Streptococcus viridans*. Petechiae were never present in the skin. Finally, the cardiac murmurs were obscured by gallop rhythm and the boy died within two weeks.

The clinical diagnosis was congenital heart disease; rheumatic heart disease; endocarditis; septicemia caused by *Streptococcus viridans* and bronchopneumonia.

The postmortem examination was performed four hours after death. The primary anatomic diagnosis was patent ductus arteriosus; hypertrophy of the heart; organizing and acute arteritis of the pulmonary artery and ductus arteriosus with thrombotic occlusion of the pulmonary bulb and ductus arteriosus; multiple infarcts of the lungs and of the spleen, and chronic splenic tumor. The subsidiary diagnosis was fibrous pleurisy and double ureter.

The bacteriologic diagnosis was *Streptococcus viridans*.

At necropsy the body was that of a fairly well nourished white boy. The skin and the sclerae had a yellow tint. No hemorrhages were noted in the skin.

Detailed drawings of the heart facilitate the description of the points of particular interest. The pericardial sac had no increased fluid. The epicardium was everywhere smooth and glistening. The estimated weight of the heart was 70 Gm. The right auricle and the right ventricle were dilated; the left heart was contracted. An irregular fusiform dilatation of the stem of the pulmonary artery was conspicuous (Fig. 1 *A*) commencing sharply about 1 cm. above the pulmonary valve. The foramen ovale was closed. The tricuspid valve measured 7 cm. in circumference; the cusps were thin and velamentous. The wall of the right ventricle was 3 mm thick. The pulmonary ring measured 5.5 cm. in circumference. The leaflets were thin. Just above the attachment of the leaflets, the stem of the pulmonary artery was filled and distended by a gray-white and red, firm thrombus with irregular surface (Fig. 1 *A*). This clot extended into both main branches of the pulmonary artery and also occluded the patent ductus arteriosus (Fig. 2 *A*), but did not extend into the aorta. The duct was 7.5 mm. long and 2.5 mm. wide. The thrombus was firmly adherent to the vessel wall except in the left posterior aspect of the pulmonary artery where the intima was smooth. The thrombus was not adherent to the wall of the ductus arteriosus except at its pulmonary orifice (Fig. 3). The mitral valve

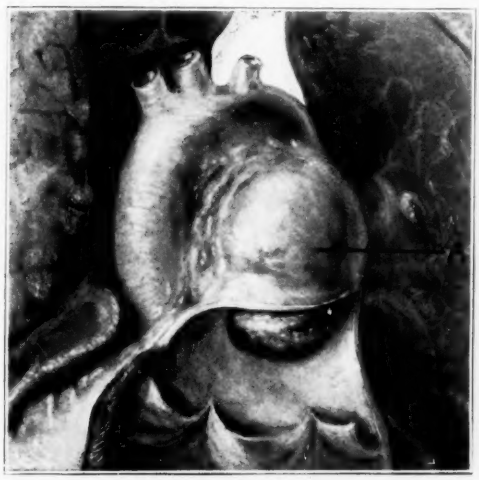

Fig. 1.—Anterior view of stem of pulmonary artery occupied by a thrombus; irregular fusiform dilatation of pulmonary bulb should be noted, *A*: lower end of thrombus and intact pulmonary valve are visible.

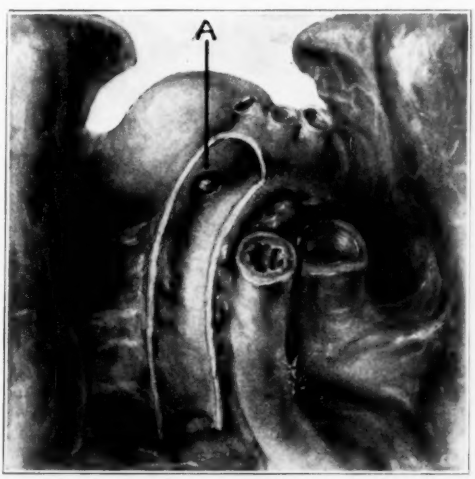

Fig. 2.—Posterior view of dilated stem of pulmonary artery and of aortic arch with the aortic orifice of ductus arteriosus occluded by a thrombus (Fig. 1 *A*).

measured 6 cm. in circumference and had thin cusps; the wall of the left ventricle was 12 mm. in thickness. The aortic ring was 5 cm. in circumference; the leaflets were thin. The bulb and the arch of the aorta had a smooth, pale yellow surface. The aorta varied in its circumference, measuring 2.8 cm. proximal to the ductus arteriosus, 3.1 cm. at the orifice, and 2.8 cm. in its descending portion. A sagittal section through the thrombus filling the pulmonary artery and the ductus arteriosus (Figs. 3 and 4) showed an irregular thickness of the wall of the pulmonary artery. The dilatation of the vessel was conspicuous and brought about an invagination of the pulmonary orifice of the

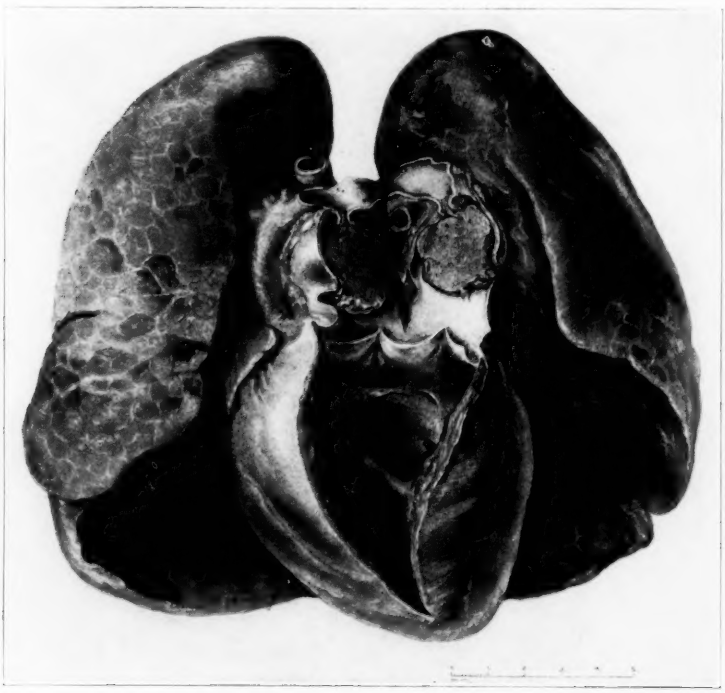

Fig. 3.—Sagittal section through thrombus occluding pulmonary bulb and ductus arteriosus; the section is prolonged into the right ventricle and exposes the intact pulmonary valve.

ductus arteriosus into the artery. The thrombus could be easily differentiated from the reddened wall of the pulmonary artery in all but three points; namely, at the juncture of the vessel with the ductus arteriosus and in two zones on the anterior wall of the pulmonary artery. In these foci the white vessel wall merged gradually into the gray thrombus.

Both lungs were quite voluminous and contained numerous dark blue, elevated, firm areas with a sharp but irregular outline separated from each other by pink crepitant lung tissue. On section these areas were irregularly wedge shaped, homogeneous, dark brown, and histologically showed the typical picture of an infected infarct.

The microscopic examination was confined to the pulmonary artery and to the ductus arteriosus and was greatly facilitated by drawings (the accompanying illustrations). By sagittal sections, a block was obtained which included in a cross section the stem of the pulmonary artery, the ductus arteriosus, and the thrombus (Fig. 4). The wall of the pulmonary artery showed an unequal involvement. In some places a diffuse cellular infiltration with mononuclear and polymorphonuclear leukocytes was noted in all the layers, extending into the perivascular tissue. The surface was generally necrotic and covered with a thrombus. These processes were particularly conspicuous at several places of the anterior wall (Fig. 5, *A*) but also were encountered in the posterior wall near the ductus arteriosus. In other places the infiltration was restricted to the intima and adjacent portions of the media. At the pulmonary orifice of the ductus arteriosus the infiltration of the whole wall was marked, diminishing

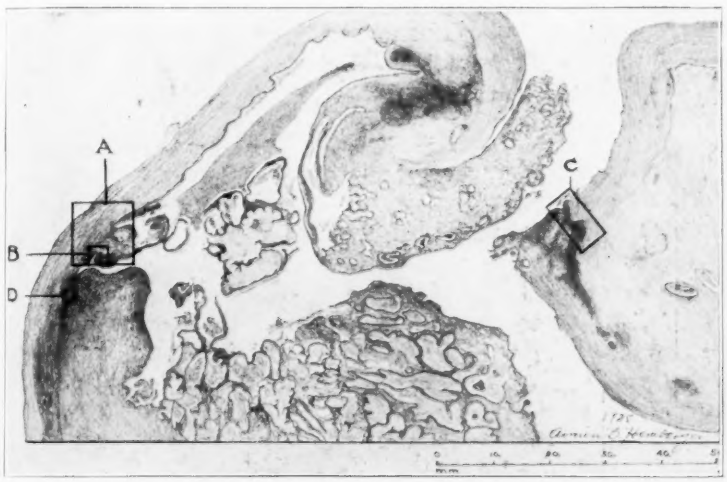

Fig. 4.—Side view of sagittal section through upper part of stem of pulmonary artery and ductus arteriosus. Squares indicate places from which areas of interest are taken and reproduced under higher power (Fig. 5).

gradually in the upper aspect of the wall of the duct, whereas in the lower part it stopped rather suddenly (Fig. 5 *C*). In the portion toward the aorta, the wall of the duct assumed a normal appearance. A moderate infiltration with mononuclear cells was present only in the loose perivascular tissue. At several places of the anterior wall in the pulmonary artery the thrombus had a warty appearance (Fig. 5 *A* and *B*) and presented the same histologic structure encountered in infectious, valvular lesions of the heart. Organization of the thrombus was encountered in several places, notably at the pulmonary orifice of the ductus arteriosus and on the anterior wall of the pulmonary artery (Fig. 5 *D*). A Gram stain of the section for bacteria was negative.

The case may be summarized: A boy, aged 8 years, who had always been well, came under observation through the school nurse for a "weak heart." The diagnosis of a patent ductus arteriosus was made. No untoward symptoms

developed until eight weeks before death when the child contracted a "cold." This was complicated by suppurative otitis media and joint pains which confined the child to bed and caused his admission to the hospital. Dyspnea was the dominant clinical feature; the heart was slightly enlarged toward the left at the apex; a soft systolic and a faint diastolic murmur were heard over the whole precordium. *Streptococcus viridans* septicemia was evident through repeated blood cultures. Necropsy confirmed the diagnosis of patent ductus

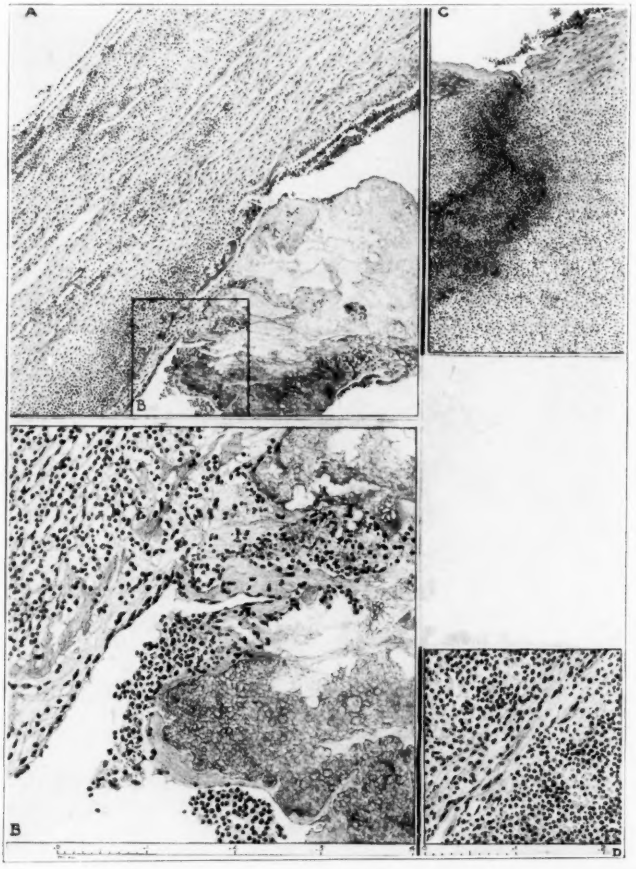

Fig. 5.—*A*, cellular infiltration involving all layers of wall of pulmonary artery; *B*, warty thrombus attached to inside of vessel wall; *C*, area of cellular infiltration at lower angle of pulmonary orifice of duct forming distinct wall of demarcation; *D*, zone taken from anterior wall of pulmonary artery where the thrombus is in process of organization.

arteriosus. Although the heart valves were normal, there was an extensive arteritis of the pulmonary bulb with thrombotic occlusion and distention of the stem and main branches of the pulmonary artery, including the patent ductus arteriosus.

REVIEW OF CASES

Of the nineteen cases on record, six occurred in males and thirteen in females. Table 1 shows the distribution among the different decades of life.

TABLE 1.—*Distribution of Cases in Decades of Life*

Decades	Number of Cases
1–10	1
11–20	4
21–30	9
31–40	4
45	1

Clinical data from the cases in the literature are entirely lacking in six instances and unequally detailed in the others. In a few instances only, the patient had subjective symptoms from his congenital heart lesion. In Sachs' [5] case and Babington's [6] case, palpitation was present from early childhood. Babington's patient (a woman, aged 34) had edema of the legs which subsided with rest. In the observations of Boldero [7] and of Murray,[8] the patients had been delicate all their lives and were not capable of ordinary work. Prior to the last illness, cyanosis was noticed in one instance. A chronic cough in Buchwald's [9] patient was explained by the chronic pulmonary tuberculosis. Sommer's patient had four labors. In our case the parents of the boy did not suspect heart disease and the boy thought himself in perfect health.

Rheumatic fever is mentioned in the past history of four cases (Murray,[8] Hochhaus,[10] Weinberger,[11] Boldero [7]). Repeated attacks of sore throat were a feature of Sommer's [12] case. In our case a double otitis media was noted shortly before the onset of the terminal illness. In reviewing the clinical findings of the heart, dilatation toward the left at the apex was noted in ten cases. In Rickards' [13] case the apex beat was felt in the sixth intercostal space. Dilatation toward the left

5. Sachs, R.: Zur Kasuistik der Gefässerkrankungen, Deutsch. med. Wchnschr. **18**:446, 1892.

6. Babington: London M. Gaz., May, 1847; Arch. gén. de méd. **17**:214, 1847.

7. Boldero, H. E. A., and Bedford, D. E.: Infective Endocarditis in Congenital Heart Disease Involving the Pulmonary Artery, Lancet **2**:749 (Oct. 11) 1924.

8. Murray, H. M.: Two Cases of Malformation of the Heart, Tr. Path. Soc. London **39**:67, 1888.

9. Buchwald: Aneurysma des Stammes der Arteria pulmonalis, Deutsch. med. Wchnschr. **4**:1, 13, 25, 1878.

10. Hochhaus, H.: Beiträge zur Pathologie des Herzens, Deutsches Arch. f. klin Med. **51**:1, 1893.

11. Weinberger, M.: Ueber periphere Verengerung der Pulmonalarterie und das klinische Zeichen derselben, Wien. klin. Wchnschr. **42**:1149, 1903.

12. Sommer, H.: Ulceröse Endocarditis mit Mitbeteiligung des offenen Ductus Botalli, Frankfurt. Ztschr. f. Path. **5**:103, 1910.

13. Rickards, E.: A Case of Ulcerative Endocarditis, Brit. M. J. **1**:640, 1889.

at the base was recorded in four; dulness in the first and in the second intercostal space at the left of the sternum is reported in the cases of Hochhaus and Hamilton-Abbott. This dulness, known as the sign of Gerhardt and due to the dilatation of the pulmonary artery, was generally confirmed by the roentgenograms through the appearance of a bottle-neck shaped shadow in the pulmonic area, which in several instances showed marked pulsation on fluoroscopic examination.[14]

In Buchwald's case, pulsation was visible not only over the apex but also in the second left intercostal space; it was wavy in character, disappearing on deep inspiration. Boldero noted a diffuse pulsation with the maximum in the second intercostal space.

In three instances (Buchwald, Hamilton, Boldero) a systolic thrill was palpable from the first to the third left intercostal space, the maximum being in the second space.

The murmur caused by the patent ductus arteriosus at the pulmonic area was loud, systolic in time, and extended into the diastole with accentuation of the second pulmonic sound. It was noted in the cases of Buchwald,[9] Foulis,[15] Rickards,[13] Murray,[8] Hochhaus,[10] Weinberger,[11] Sommer,[12] Hamilton,[2] Boldero,[7] and in our case. Rickards and Foulis described it as a double murmur. In our case a soft systolic and a faint diastolic murmur was heard over the whole precordium. The murmur was transmitted upward into the left carotid and the left subclavian artery. According to Frank, it was not transmitted to the back. Boldero, however, states that in his case the murmur was harsh and continuous also in the back of the chest. In the case of Boldero (a man, aged 29) the blood pressure was 200 systolic, 90 diastolic. The Wassermann reaction, recorded in our observation only, was negative.

The duration of the terminal illness with fatal outcome varied between two months (Buchwald, Hamilton) and two years in Boldero's case. The course was always progressive; the picture was that of an acute or subacute blood stream infection with intermittent fever accompanied with heart symptoms of variable degree. Death occurred from cardiac failure. The blood culture revealed *Streptococcus viridans* in Terplan's[16] and in our case; Hochhaus[10] recovered *Staphylococcus albus;* Schlagenhaufer,[17] influenza bacilli, and Hamilton and Abbott,[2] pneumococci.

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14. Wessler and Bass, cited by Hamilton and Abbott (Footnote 2).

15. Foulis, J.: On a Case of Patent Ductus Arteriosus with Aneurysm of the Pulmonary Artery, Edinburgh M. J. **30**:17, 1884.

16. Terplan, K.: Mykotisches Aneurysma des Stammes der Pulmonalarterie mit Endocarditis des offenen Ductus Botalli bei einem Falle von Endocarditis lenta, Med. Klin. **20**:1331, 1924.

17. Schlagenhaufer, F.: Ein Fall von Influenza-endocarditis der Aortenklappen und des offenen Ductus Botalli, Ztschr. f. Heilk. **22**:19, 1901.

ANALYSIS OF NECROPSY FINDINGS

In the observation of Terplan and of Krzyszkowski, an exudate was present in the pericardial sac, serofibrinous in one and hemorrhagic in the other.

Dilatation and hypertrophy of the heart were mentioned in almost all instances, hypertrophy involving both sides, dilatation being restricted to the right heart. The thickness of the right heart muscle varied between 0.3 cm. in our 8 year old boy and 1 cm. in Sommer's 45 year old woman. Boldero's [7] 29 year old man also had a heart wall 1 cm. in thickness.

Examination of the mitral valve revealed fresh vegetations in five instances (Babington, Buchwald, Foulis, Murray, Hochhaus). Weinberger [11] reported a chronic lesion of the ring and three authors (Sachs,[5] Hart,[18] Case 2, Sommer [12]) mentioned merely a thickening of the cusps, pointing to a healed process.

The aortic valve was damaged in thirteen out of the nineteen cases. The nine observations in which the mitral orifice was inflamed also showed a lesion of the aortic valve. The aortic vegetations were the only lesion in the left heart in the cases of Kidd,[19] Schlagenhaufer,[17] Hart,[18] Case 1, Terplan,[16] and Boldero.[7] In all instances the lesions were acute except in Babington's [6] patient (a woman, aged 34) in whom the ring was stenosed by calcified vegetations.

The tricuspid valve was bordered by fresh vegetations in Murray's [8] case with similar lesions on the mitral and the aortic valve. Vegetations on the pulmonary valve were found in nine cases. In all instances the stem of the pulmonary artery and the patent ductus arteriosus were the seat of an arteritis with thrombus formation. In the remaining ten cases the pulmonary valve was normal but the pulmonary artery and the ductus arteriosus showed a more or less extensive inflammation. Three cases of this second group, including ours, are unusual as far as the arteritis was not complicated by any valvular endocarditis.

The points of interest are the extent and the character of the lesions in the pulmonary artery with the possible dilatation resulting from the chronic inflammation and the changes observed in the ductus arteriosus. We shall first review the findings in the pulmonary artery of the cases with a pulmonary or other valvular lesion, then analyze separately the observations of the three cases without any complicating endocarditis. Finally, the anatomic findings in the patent ductus arteriosus will be

18. Hart, C.: Ulceröse Endocarditis mit Mitbeteiligung des offenen Ductus Botalli, Virchows Arch. f. path. Anat. **177**:218, 1904.

19. Kidd, Percy: Embolic Aneurysm of Pulmonary Artery; Infective Aortic Valvulitis, Aortitis and Pulmonary Endocarditis; Patent Ductus Arteriosus, Tr. Path. Soc., London **44**:47, 1893.

TABLE 2.—*Summary of Cases*

Author and Year of Publication	Sex* and Age	Clinical Data †	Condition of Heart Valves ‡	Condition of Pulmonary Artery	Form and Condition of Ductus Arteriosus	Bacteriology	Remarks
Babington..... 1847	♀ 34	P.H. Palpitation since childhood; no rheumatism	M. Fresh vegetations A. Vegetations in part calcified	Fusiform dilatation of stem	Funnel shape, widely patent; small vegetations at pulmonary orifice	?	Infarcts of lungs
Buchwald..... 1878	♀ 21	P.H. Chronic cough; pulmonary tuberculosis	P. Numerous vegetations M. Fresh vegetations A. Fresh vegetations	Trianglar area on anterior wall from valve to duct occupied by thrombus	Funnel shape; vegetations on both openings	?	Forked embolus in branch of lower left lobe of lung
Foulis..... 1884	♀ 22	P.H. Scarlet fever at 16; no rheumatic fever	P. Vegetations on leaflets M. Verrucose vegetations A. Full of vegetations	Thrombi on left side of wall partly filling great aneurysm covering left auricular appendage	Funnel shape; pulmonary orifice occupied by thrombus	?	Infected thrombi in branches of pulmonary artery
Murray..... 1888	♀ 36	P.H. Always delicate; rheumatic fever at 26 P.I. Malignant endocarditis	T. Vegetations on free border M. Vegetations ..... A. Vegetations	Anterior wall up to duct covered with thrombus	Funnel shape; thrombus at pulmonary orifice; aortic mouth shows calcium deposit	?	Infarcts of spleen and kidney
Rickards..... 1889	♂ 17	P.H. Always thin and pale	P. Polypoid vegetations	Partially occluded by thrombus up to pulmonary orifice of duct	Vegetations around pulmonary orifice	Micrococci	Infarcts of lungs and kidneys; vegetations on aortic wall opposite duct
Sachs..... 1892	♀ 21	P.H. Palpitation since childhood P.I. Malignant endocarditis	P. Verrucose vegetations M. Slightly thickened A. Extensive vegetations	Longitudinal rows of thrombi on anterior wall throughout whole length	Funnel shape; thrombus occluding pulmonary orifice	?	Infarcts of lung and spleen; aneurysm with thrombi in branches of pulmonary artery; amyloid degeneration of spleen, liver, kidney, intestine
Hochhaus..... 1893	♂ 24	P.H. Rheumatic fever at age of 12 P.I. Recurrent malignant endocarditis	P. Vegetations ..... M. Vegetations A. Vegetations	Small, cauliflower-like vegetations up to duct	Funnel shape; vegetations around pulmonary orifice	Staphylococcus albus	Infarcts of lung and spleen; vegetations opposite orifice of ductus arteriosus
Kidd..... 1893	♀ 22	P.I. Dyspnea	P. Healthy ..... A. Large soft vegetations	Crop of warty fibrinous vegetations on posterior wall	Fibrinous vegetations on aortic orifice	?	Aneurysm of branch of left pulmonary artery surrounded by healthy lung tissue; in aorta saccular aneurysm near duct
Gauchery..... 1900	♀ 27	No data	P. Vegetations	Thrombus from valve to duct; fusiform dilatation of stem	Vegetations forming fringe around pulmonary orifice and in duct	?	Multiple septic emboli, organs not mentioned
Schlagenhaufer..... 1901	♂ 13	P.I. Subacute bacterial endocarditis	A. Vegetations	Numerous vegetations in whole bulb	Both orifices and duct covered with vegetations	Influenza bacilli	Multiple infarcts of lungs
Krzyszkowski..... 1902	♀ 17	P.I. Hemoptysis	Normal	Fusiform dilatation; thrombus adherent to anterior wall	Funnel shape; pulmonary orifice occupied by thrombus	?	Infarcts of lungs; aneurysms of smaller branches of pulmonary artery

TABLE 2.—*Summary of Cases—(Continued)*

TABLE 2.—*Summary of Cases—(Continued)*

Weinberger..... 1903	♀ 37	P.H. Rheumatic fever	P. Numerous vegetations M. Chronic lesion A. No vegetations	Scattered thrombi on anterior wall	Aortic orifice and duct lined with vegetations	?	
Hart (I)..... 1904	♂ 23	P.I. Anemia; intermittent fever	A. Red vegetations..	Vegetations forming lines from duct to valve	Funnel shape; duct and pulmonary orifice covered with small vegetations	?	Infarcts of heart, kidneys, stomach, spleen, intestine; hemorrhagic nephritis
Hart (II)..... 1904	♀ 24	P.I. Anemia	M. Thickening ..... A. Cauliflower, pink vegetations in sinus of Valsalva	Riddled with small vegetations extending into branches of pulmonary artery	Duct filled with pin point vegetations	? Not determined	Infarcts of lungs, kidneys, spleen, heart
Sommer... 1910	♀ 45	P.H. Repeated angina P.I. Dyspnea and edema of legs for 9 months	P. Vegetations on anterior leaflet M. Thickened; no fresh vegetations A. Ulcerative vegetations	Numerous thrombi from duct to valve	Funnel shape; pulmonary orifice narrowed by vegetations	?	Infarcts of lungs, spleen and kidney
Hamilton and Abbott 1914	♀ 19	P.H. Pale and slender P.I. Symptoms of general infection for 2 months	Normal	Thrombus on anterior wall extending into left branch (pulmonary bulb dilated)	Vegetations around pulmonary orifice and adjacent part of duct	Pneumococci	Embolic abscesses in both lungs; narrowing of aorta below ductus arteriosus
Terplan..... 1924	♀ 35	P.I. Arthritis of spine	M. Chronic ..... A. Large ulcerative vegetations	Thrombus on anterior wall throughout whole length (pulmonary bulb dilated)	Both openings filled with vegetations	Streptococcus viridans	Infarcts of spleen; hemorrhagic glomerular nephritis; peritonitis with hemorrhage in peritoneum
Boldero and Bedford.. 1924	♂ 29	P.H. Always delicate; rheumatic fever in childhood; diphtheria at 7	P. Extensive vegetations A. Covered with vegetations	Numerous warty vegetations on anterior wall throughout whole length	Duct filled with small warty vegetations	?	No infarcts of lungs; embolic glomerular nephritis
Schlaepfer..... 1926	♂ 8	P.H. No rheumatism P.I. Double otitis media	Normal	Fusiform dilatation of stem; on anterior and right side, adherent thrombus filling lumen	Thrombus adherent to pulmonary orifice filled duct	Streptococcus viridans	Infarcts of lungs and spleen
Rauchfuss, C. 1859	♂ 8 days	Omphalitis; septicemia	.....	.....	Patent ductus occluded by partly puriform, softened thrombus	.....	No emboli mentioned
Rauchfuss, C. 1859	♀ 10 days	At 8 days, erysipelas starting at umbilicus and spreading	.....	.....	Duct 15 mm. long filled with thrombi protruding through pulmonary orifice into pulmonary artery; not protruding into aorta	.....	Infarcts of lungs; petechial hemorrhages in intestines; pus in joints; infected thrombi in umbilical vessels
Rauchfuss, C. 1859	♀ 16 days	Omphalitis; arthritis; cerebrospinal meningitis	.....	.....	Duct 17 mm. long and 5 mm. in diameter partly filled by softened thrombus; not protruding into aorta	.....	No emboli mentioned
Rauchfuss, C. 1859	♀ 19 days	Enteritis	.....	From duct, extending into right branch	Funnel shape; filled by thrombus protruding into aorta	.....	Emboli in lungs and kidneys; infection of umbilical cord not demonstrated

* In this table, ♂ indicates male; ♀, female.
† P.H., past history; P.I., present illness.
‡ T., tricuspid; P., pulmonary; M., mitral; A., aortic.

summarized and the nature and the extent of the inflammatory lesion in this anomaly of the heart reviewed.

In the cases with a pulmonary or other valvular lesion the arteritis in the pulmonary artery was always accompanied with thrombosis. The thrombus generally involved the anterior wall of the artery. In Foulis' case the thrombus was more adherent to the left side of the stem of the pulmonary artery. Kidd found a crop of warty vegetations attached to the posterior side of the pulmonary artery. He is the only author who does not stress the fact that the anterior and the upper walls of the stem of the pulmonary artery were the seats of inflammation. In all instances the vegetations were described as soft and polypoid. Boldero noted that in his case the thrombus completely occupied the lumen of the vessel. In Buchwald's observation, there was a triangular area of attachment of the thrombus with the base at the pulmonary valve and the apex at the ductus arteriosus. Rickards' patient also had a thrombus adherent to the anterior wall partly occluding the lumen of the pulmonary artery. Numerous small thrombi adherent to the wall of the pulmonary artery were reported by Hochhaus, Gauchery [20] and Sommer. Sachs and Foulis had lines of thrombi forming crests of irregular thicknesses from the valve to the ductus arteriosus. In Hart's first case the vegetations formed lines; in his second case stem and branches of the pulmonalis were riddled with pinpoint sized vegetations. Also Schlagenhaufer and Weinberger found numerous small vegetations in the pulmonary artery. In Murray's case the thrombi formed an oval mass on the anterior and upper aspect of the dilated artery. In Terplan's case, the thrombus occupied a large part of the pulmonary artery.

The following three cases are reviewed separately because the pulmonary artery with the patent ductus arteriosus were the only seats of inflammation: In Krzyszkowski's case, 2.5 cm. above the valve the anterior wall of the pulmonary artery and its left main branch were occluded by a thrombus. Hamilton and Abbott found the pulmonary artery occupied by a large, moist gray thrombus attached to the anterior and upper wall. Pyramidal in shape, the thrombus had its broad base vertically in the lumen of the pulmonary artery, leaving the right half of the stem and the right main branch free. The central end of the thrombus was situated 1 cm. from the pulmonary valve. With its upper end, the mouth of the ductus arteriosus was plugged. In our case the pulmonary artery and both main branches were filled by a gray-white and red thrombus. It was adherent to the wall except in the posterior left aspect of the pulmonary bulb.

20. Gauchery, F.: Persistenz des Ductus Botalli, Endocarditis ulcerosa der Arteria pulmonalis und aneurysmatische Erweiterung des Anfangteiles d. Pulmonalis, Centralbl. f. allg. Pathol. u. path. Anat. **2**: 70, 1900.

The chronic infection of the arterial wall produced in many instances of arteritis of the pulmonary artery a fusiform dilatation at the site of greatest damage. Terplan mentioned a dilatation in the area of attachment of the thrombus to the vessel wall. Krzyszkowski and Hamilton noted a fusiform dilatation of the pulmonary bulb, also observed in our case. Foulis reported a dilatation to the left with the result that the aneurysm covered the left auricular appendage.

The anatomic findings in the duct may be summarized: In eight instances the patent ductus arteriosus had a funnel shape with a narrowing of its pulmonary orifice. In others, as in ours, the canal had about the same caliber throughout. The length and the width of the duct varied. Boldero mentioned 1.5 cm. as the length in his 29 year old man; Hamilton-Abbott, 7.5 mm. (a woman, aged 19). In our patient (a boy, aged 8) the duct measured 7.5 mm. Hochhaus' figure is 6 mm. (a man, aged 24); Schlagenhaufer gives 5 mm. (a boy, aged 13 years); Sachs, 3 mm. (a woman, aged 21). Babington called the duct in his 34 year old woman, widely patent. Foulis and Murray could pass a goose quill; Sachs measured 3 mm. width; Schlagenhaufer, 4 mm.; we found 2.5 mm.

The extent of the arteritis in the ductus arteriosus varied in the different observations. In eleven of the nineteen cases, the pulmonary orifice alone was the seat of thrombi filling the duct in part (Hamilton) or completely (Schlaepfer) without any evidence of attachment to the wall except at the pulmonary orifice. Also in Krzyszkowski's observation, the pulmonary orifice was the only affected part. Microscopically, in our case, the wall was involved for only a short distance at the pulmonary mouth, whereas in Hamilton's case the wall was inflamed in its whole length. Hamilton mentioned a calcified lymph node which was adherent to the outside of the wall. In three instances (Buchwald, Kidd, Terplan) both orifices of the duct were fringed with vegetations; no notes were found about the condition of the duct itself. In five cases (Schlagenhaufer, Hart, Cases 1 and 2, Weinberger, Boldero) small, warty vegetations narrowed the lumen of the duct.

Some findings of note deal with changes in the aorta in the vicinity of the opening of the duct. In Foulis' case, a saccular aneurysm with atheromatous changes was found opposite the mouth of the duct. An analogous observation was noted by Hochhaus. The inside of the sac was filled with small thrombi which were adherent to the wall. Rickards noticed similar adherent thrombi in the same location without any aneurysm formation. This part of the aorta was attached to the trachea. Babington mentioned atheromatous changes in the aorta opposite the duct.

A fold arising from the aortic wall central to the opening of the duct, protruding into the lumen of the aorta, was noted by Babington, Buchwald and Hochhaus. Babington mentioned in addition a narrowing of the descending portion of the aorta. Hamilton in his case also found a narrowing of the descending aorta (coarctation). Our patient showed a slight dilatation of the aorta beyond the aortic orifice of the duct; further down the aorta was normal.

The necropsy findings in the other organs of the nineteen cases are of interest as they were the result of thrombi broken off from a valve, the pulmonary artery, or the patent duct. As infected thrombi, they produced infarcts and inflammation in the lungs, the spleen, the kidneys, the intestines, the skin and the brain. The lungs were the seat of multiple infarcts in thirteen cases. In some instances the process had progressed to abscess formation. A rather peculiar feature was the formation of saccular aneurysms in the smaller branches of the pulmonary artery (Sachs, Kidd, Krzyszkowski). In nine cases infarcts of the spleen were mentioned, of the kidneys in seven.

COMMENT

In instances of arteritis of the pulmonary artery associated with patent ductus arteriosus, the clinical symptoms and signs of a patent duct persist but may become complicated and masked by the infectious process and occlusion of the duct by a thrombus. The signs of a patent duct may be summarized as follows: (1) dulness in the first and in the second left intercostal space next to the sternum (Gerhardt); (2) enlarged pulmonary artery in the form of a bottle neck shaped shadow in the roentgenogram; (3) pulsation in the area of dilatation on fluoroscopic examination; (4) enlarged cardiac dulness at the apex associated with ventricular dilatation and hypertrophy; (5) visible pulsation at the apex especially on deep expiration, or a palpable thrill over the apex which is also felt in the second left intercostal space and at the jugular notch; (6) a loud systolic murmur extending into the diastole with accentuation of the second pulmonary sound, best heard in the pulmonic area, but transmitted from there to the neck and to the left arm but generally not into the back. The signs of a superimposed arteritis can only be assumed from the presence of the well known signs of a subacute bacterial endocarditis. The infarcts in various organs, such as the lung, the spleen and the kidneys, and in the skin may help to make an accurate diagnosis.

The pathology of the cases reviewed in this article shows that dilatation and hypertrophy of the heart results and is particularly marked in the right side. This is the mechanism whereby the difference in pressure in the aorta and in the pulmonary artery is brought to an equilibrium.

The normal ratio of the pressure in the aorta and in the pulmonary artery is 5:2 according to Goltz-Gaule, and 3:1 according to Marey. The difference in pressure is met by the muscular hypertrophy of the right side. The diameter of the lumen of the patent ductus arteriosus is a determining factor for the blood flow.

In sixteen out of nineteen cases, some valvular lesions of the heart were present. In these cases and in the three others put together in a special group, the pulmonary artery and the ductus arteriosus were the seat of a chronic arteritis. It may be interesting to note the interpretation given by previous observers of such lesions and see how they correlated the different findings. The explanation will vary somewhat according to the group of lesions present in a given personal observation.

Mechanical injury to the wall of the pulmonary artery by the constant blood flow from the aorta through the ductus arteriosus was, according to Foulis, the main factor for the formation of an aneurysm in his case. Foulis did not stress the presence of infection in the arterial wall. Weigert-Sachs first emphasized the predisposition of circumscribed portions of the pulmonary artery to arteritis by the mechanical traumatism of an abnormal blood flow from the aorta through the patent duct. Sommer also took up this explanation for the localization of the thrombo-arteritis on the anterior wall of the pulmonary bulb in the prolongation of the long axis of the duct. Hamilton and Abbott mentioned the possibility of infected emboli in the vasa vasorum of the affected portion of the pulmonary artery. In minute tears of the intima resulting from mechanical strain, an infection with subsequent thrombosis may start through circulating micro-organisms.

Generally the way of infection is assumed to take place by a blood flow from the aorta through the duct into the pulmonary artery. Buchwald and Weinberger assumed in their case first a lesion of the pulmonary valve and from there a propagation into the pulmonary artery. This argument holds true for only a group of cases.

The fusiform dilatation of the pulmonary artery observed in many of these cases is the result of the weakening of the wall in the presence of a chronic infection. Posselt,[21] however, showed that in many cases of patent ductus arteriosus without any complicating arteritis a dilatation of the pulmonary artery is frequently encountered.

The funnel shape of the ductus arteriosus at its aortic orifice may partly be explained by the relative absence of elastic fibers in the media, as demonstrated by Busse.[22] On the same basis Busse explains the

21. Posselt: Die Erkrankungen der Lungenschlagader, Lubarsch-Ostertag, Ergebn. d. allg. Pathol. u. path. Anat. **13**:352, 1909.

22. Busse, O.: Zur normalen und pathologischen Anatomie des Ductus Botalli, Cor.-Bl. f. schweiz. Aerzte **48**:457, 1918.

frequency of atheromatous changes in this location. In a review of cases of patent duct Rokitansky [23] found the duct funnel shaped in most instances; in only a few cases was the duct short with a uniform, large lumen throughout. In all cases Rokitansky observed a dilatation and hypertrophy of the right ventricle. Some hypertrophy also was present in the left heart. Repeatedly he noticed a narrowing in the descending portion of the aorta, as encountered by Hamilton and Abbott.

The four cases of Rauchfuss with thrombosis of the arterial duct in new-born infants are unique and stimulate a more careful examination of the duct when necropsies are being performed on babies.

SUMMARY

Chronic and acute arteritis of the pulmonary artery and of the patent ductus arteriosus has been observed in nineteen cases. To two of these cases in which no additional valvular lesions were found, a third is added.

In all nineteen cases, the picture was that of a subacute bacterial endocarditis with the signs of a patent ductus arteriosus.

The seat of the arteritis is undetermined. Satisfactory evidence is not at hand to determine the influence of the force of the blood flow passing from the aorta through the duct into the pulmonary artery. The anterior wall of the pulmonary artery and the pulmonary orifice of the duct are the places of predilection.

Dilatation of the stem of the pulmonary artery is often accompanied with a patent ductus arteriosus; in cases of arteritis, an aneurysmal bulging results at the site of the thrombus on the vessel wall.

Narrowing (coarctation) of the descending aorta is an anomaly frequently associated with patent ductus arteriosus. It facilitates the blood flow through the duct and thereby increases the traumatism to a circumscribed part of the anterior wall of the pulmonary artery.

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23. Rokitansky, C.: Ueber Persistenz des Dustus areriosus, Ztschr. f. d. Gesellsch. d. Aerzte in Wien. **1**:137, 1864.

THE POSSIBLE RELATIONSHIP BETWEEN ACROMEGALY AND DIABETES

WITH REPORT OF THREE CASES *

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According to the figures given by various authors, diabetes occurs in from 10 to 40 per cent of the cases of acromegaly. Even the lowest of these figures is sufficiently high to suggest that this is more than a coincidence, that there must be some common factor underlying both conditions. In going over the older literature one finds that most of the diagnoses of diabetes in these cases have been made on the basis of the urinary examinations for sugar. In considering this subject, therefore, we must bear this point in mind for in the light of more recent work we know that glycosuria is not always a true indication of diabetes.

In an analysis of all cases of pituitary disease which have been seen at the Cleveland Clinic, comprising forty-one cases to date, seven cases of acromegaly were found, diabetes being present in two of these, 28.5 per cent. Were we to consider pituitary tumor as a causative factor in the production of diabetes, then we might suppose that the opposite clinical entity, namely, hypopituitary disease, would be marked by an increased carbohydrate tolerance. Of the forty-one cases of hypopituitary disease referred to above, there was no glycosuria in twenty-six, and in five there was more or less marked diabetes; thus, 16 per cent of this group showed a decreased carbohydrate tolerance. If acromegaly, which is due to hyperpituitarism, produces diabetes, on the other hand the reverse condition, hypopituitarism, certainly does not offer any protection against diabetes.

Diabetes in cases in which either hyperpituitarism or hypopituitarism also is present does not differ from diabetes in cases in which these disturbances of pituitary function are not present. Moreover, the removal of the pituitary gland certainly does not cure a case of diabetes, and no authentic case of cure by such means has ever been reported in the literature. That the secretion of the pars posterior and the pars intermedia has something to do with carbohydrate metabolism is shown by the fact, as has been reported in the literature, that injection of pituitary extract (pars posterior) causes hyperglycemia and glycosuria. It would appear, therefore, that hypertrophy of the gland ought in part to have the same effect as injection of the extract, although the effect

* From the Cleveland Clinic.

of the former should depend largely on the functional activity of the posterior and possibly of the intermediate lobes rather than on the size of the tumor.

Against the hypothesis that the pituitary gland is the sole factor in disturbances of carbohydrate metabolism may be cited the fact that removal of the pituitary tumor does not cure diabetes. It may improve the condition, as some observations seem to indicate, but the data are not conclusive, as in the literature glycosuria is not fully differentiated from true diabetes. Moreover, in cases in which the patients are reported to have improved or recovered after removal of the pituitary gland, it may be that the diabetes had merely been held in check by strict adherence to the appropriate diet. Just such a status is frequently seen in cases of diabetes in which a marked hyperglycemia is present when the patients are on a moderate diet, but if the condition has been brought under control they can take a much higher diet without any increase in the blood sugar beyond the normal range. Whether this changed status is due to a functional improvement of the insulogenic function or to regeneration of the islands of Langerhans is not known.

The following two cases, in each of which diabetes developed years after the acromegaly was recognized, illustrate the fact that diabetes associated with acromegaly does not differ materially, as far as we can observe, from diabetes without acromegaly; that the same treatment is applicable to the former as to the latter types of cases of diabetes; that in each the same results may be expected under proper treatment; and that in each case, if the patient is untreated or is improperly treated, the same increased loss of carbohydrate tolerance, acidosis and coma ensues.

REPORT OF CASES

CASE 1.—A man, aged 55, came to the Cleveland Clinic in March, 1925, complaining of general weakness, intense thirst and polyuria. The patient had had none of the diseases of childhood but had had pneumonia and rheumatism in later life. At the age of 22 his head had been injured and his leg broken in an accident. In 1924 he had had some teeth extracted. Apart from his rheumatism, he had been fairly well until December, 1924, about three months before I saw him, when he had an attack of hiccups which lasted for five days, and glycosuria was discovered by his family physician, who had been treating him with insulin. At times he had double vision and his eyelids drooped a little. He had some dyspnea on exertion and his rectum frequently prolapsed. During the preceding three months he had lost 37 pounds (16.8 Kg.)

Physical examination disclosed a tall man, 6 feet, 1 inch (185.4 cm.) in height, weighing 203 pounds (92.1 Kg.), with coarse features and large joints and fingers of the acromegalic type (Figs. 1 and 2). There was marked hypertrophic arthritis of the hands and roentgen-ray examination revealed Heberden's nodes on the fingers (Fig. 3). The pulse rate was 104, blood pressue 105 systolic, 78 diastolic. The scalp was very thick and wrinkled, with protruding supraorbital ridges; the cheeks and jaw were very prominent.

The growth of the skull, the hands and the feet during the preceding ten years is shown by the following comparative measurements:

	Hat	Glove	Shoe	Shirt
1915	7⅜″	No. 10	No. 9	16.5
1925	7⅝″	No. 13	No. 12	17.5

Roentgen-ray examination showed a large sella turcica (Fig. 4).

Laboratory findings were as follows: *Urine:* sugar, 5 per cent; acetone, 4 plus; diacetic acid, plus; trace of albumin; few hyaline casts. *Blood:* red blood cells, 4,550,000; white blood cells, 5,900; hemoglobin, 85 per cent.

In this case it was not necessary to make a glucose tolerance test in order to confirm the diagnosis of diabetes, as the presence of a 5 per cent glycosuria with a fasting blood sugar value of 440 mg. per hundred cubic centimeters is sufficient evidence of the condition; but in view of the statements by his physician that neither insulin nor a month's treatment with pituitary extract had benefited him at all, the glucose tolerance test was made for final proof (Table 1 and Fig. 5).

TABLE 1.—*Glucose Tolerance Test on Day After Admission*

	Blood Sugar Before and After Ingestion of 100 Gm. of Glucose in Mg. per 100 Cc.	Sugar in Urine in Gm.
Before	440	3 plus
One-half hour after	543	....
One hour after	626	6.27
Two hours after	680	17.5
Three hours after	600	12.0
Four hours after	506	11.5

Total water intake, 860 cc. Total sugar intake, 100 Gm.
Total urine output, 1,010 cc. Total sugar output, 47.27 Gm.

Corpuscle volume at start, 36 per cent	Mg. per 100 Cc.
Plasma chlorids	530
Blood urea	51
Blood uric acid	2.7
Blood creatinin	1.6
Nonprotein nitrogen	55.6
Plasma acetone, trace	

It was evident that the prime need was to treat the diabetic condition. The patient was therefore placed in our diabetic hospital, on a diet of 100 Gm. of carbohydrate, 60 Gm. of protein, and 128 Gm. of fat, a total of 1,800 calories, on which he gained 5 pounds (2.3 Kg.) during the first twenty-four days, but later lost 10 pounds (4.5 Kg.). He received an average of 100 units of insulin per day in four doses, 40, 20, 20 and 20 units, respectively, for ten days, at the end of which time his blood sugar had reached the normal level. He then received 20 units per day for about two weeks and only three doses after that. April 17, his diet was increased to 120 Gm. of carbohydrate, 80 Gm. of protein, 133 Gm. of fat, a total of 2,000 calories, and the insulin was discontinued. As Figure 6 indicates, he kept a normal blood sugar level until he was discharged, April 29. The twenty-four hour sugar output in the urine was as follows: March 25, 78.75 Gm.; March 26, 27.00 Gm.; March 27, 1.54 Gm.; March 28-30, trace; after March 31, none.

A double iridectomy was performed on April 17, as he had developed acute cataracts in both eyes; one lens was removed a few days later. The cataracts had developed rapidly, for when the patient entered the clinic the lenses were clear, but within a few days a lenticular change began, the progress of which could be seen from day to day, a surprising circumstance, as one would expect that the control of the diabetic condition would prevent any further retrogressive eye changes. The visual fields could not be measured on account of the cataracts.

The report of Dr. A. D. Ruedemann of the ophthalmologic department of the clinic was as follows:

3/20/25. Vision right eye on entrance, 6/15; vision left eye on entrance, 6/20.
Improved with a plus 2 lens to 6/10; tension (Schiötz) 25 in both eyes. The examination revealed early lenticular changes in both eyes with no changes in the disk or retina.

4/ 3/25. Heavy central opacities, vision reduced to 6/60, not improved with glasses. No changes in the fundus. Fields of vision could not be taken on account of the opacities in the lenses.

4/17/25. Double iridectomy was performed, which did not materially improve the vision, so the right lens was extracted.

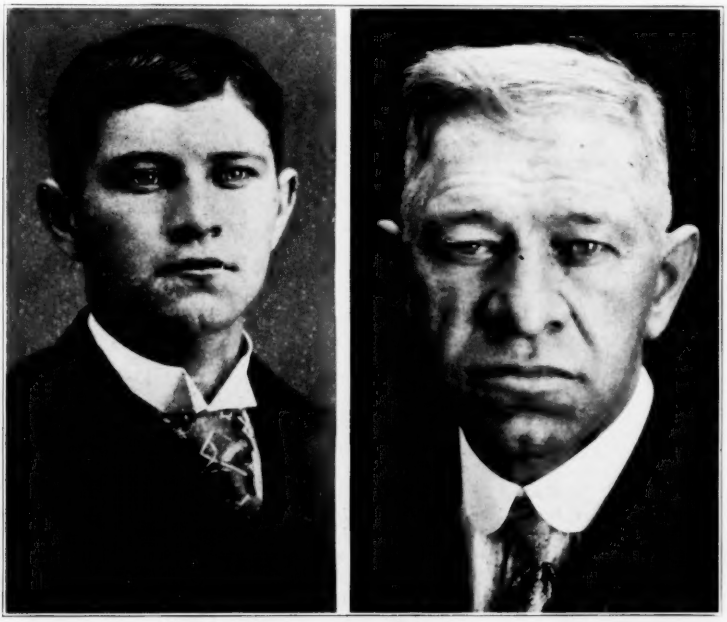

Fig. 1.—Patient with acromegaly associated with diabetes, showing development of acromegalic features.

The patient was seen by me again nearly three months later. During the interim, he had been living on a liberal diet; practically the only things he had eliminated were sugar and pastry. At this time, his fasting blood sugar was 105 mg. per hundred cubic centimeters, and there was no glycosuria present. A glucose tolerance test was then made, which, to my astonishment, gave a normal curve, the first normal curve in a diabetic case that I have ever encountered (Fig. 7). The clinical progress together with the fasting blood sugar level suggested a marked improvement, but the glucose tolerance test demonstrated that the functional capacity of the island tissue had been restored to normal. In other words, the diabetic condition had been cured. The question which remains unanswered is, Is this a permanent cure, or under some undue strain, will the pancreas again break down? This naturally cannot be answered at

this stage, but we hope to be able to follow this patient; if in a decade or two he still remains normal, this will be an authentic case of a permanent cure of diabetes.

This is a typical case of the association of diabetes with acromegaly. Because of the acromegaly the diabetic status had not been recognized, the polyuria being considered to be due to the pituitary condition,

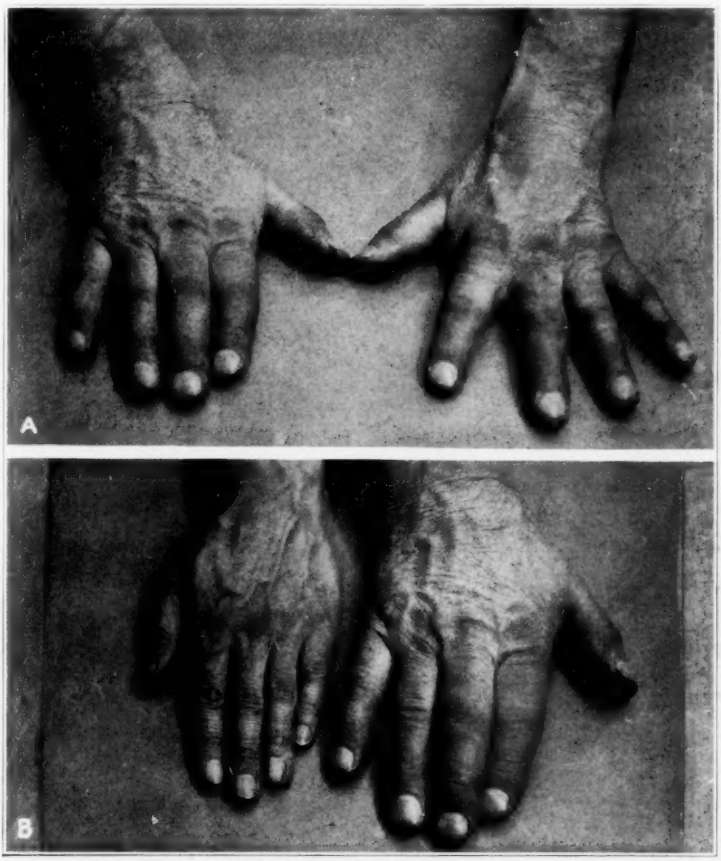

Fig. 2.—*A*, acromegalic hands of patient shown in Figure 1; *B*, acromegalic hand of same patient compared with normal hand.

although pituitary extract did not improve the condition, which grew worse daily.

In this patient the acromegaly preceded the diabetes by ten years. It does not seem probable that if acromegaly, or hyperfunction of the

hypophysis, causes diabetes, it could be present for ten years without exerting any apparent influence on the metabolism of carbohydrates and then suddenly produce diabetes. It would appear more probable that ten years after the initiation of the acromegaly, some other factor was introduced which produced the diabetes. Was it the rheumatism

Fig. 3.—Acromegalic hand of patient shown in Figure 1, showing hypertrophic arthritis of hand and Heberden's nodes on fingers.

or was there a prediabetic status which, due to his heavy overeating, precipitated the diabetes?

CASE 2.—A woman, aged 41, having no familial history of diabetes, had acromegaly, which had developed twelve years before. Besides this she had had no previous illnesses except measles and influenza. Menopause occurred at the age of 37.

Glycosuria had been first discovered four years before I saw her, but other diabetic symptoms, itching of the genitalia, polyuria and thirst, had not developed until two years later. During these two years her weight had fallen from 198 to 135 pounds (89.8 to 61.2 Kg.).

Physical examination disclosed the following conditions which are of especial interest: Acromegalic facies, hypertrophied labia, small uterus, deep masculine voice, thick lips, wide shoulders, narrow hips, much enlarged hands and feet.

When she entered the diabetic hospital of the Cleveland Clinic her blood sugar was 400 mg. per hundred cubic centimeters and she had a glycosuria of 8 per cent. The Wassermann reaction was negative. A phenolsulphonephthalein kidney functional test showed an excretion of 40 per cent during the first hour, 20 per cent the second.

Fig. 4.—Skull of patient shown in Figure 1, showing large sella turcica.

The graphic record (Fig. 8) shows how a regulated diet plus insulin reduced the blood sugar to the normal level in two weeks, during which time the twenty-four hour urine sugar, which at first was as much as 56 Gm., disappeared entirely.

From time to time after her discharge from the hospital, friends of the patient reported to me that she would not adhere to the prescribed diet but was eating as she pleased and was not taking insulin regularly.

Fifteen months later I was called to see her at another hospital by a physician who had been summoned to take care of her some ten days previously because of a carbuncle which had developed on her buttock. At the time I saw her she was in deep coma, with blood sugar varying from 475 mg. per hundred cubic centimeters in the morning to 810 mg. the afternoon of the same day; heavy acetonemia was present and the plasma carbon dioxid amounted to a tension of 9.9 mm.

A 10 per cent glucose solution with insulin was administered intravenously; the patient rallied a little but died on the second day from acute dilatation of the heart, which developed when she began to struggle in an attempt to sit up.

In this case, as in Case 1, acromegaly had preceded diabetes by a number of years and, as in the former case, we cannot say whether or

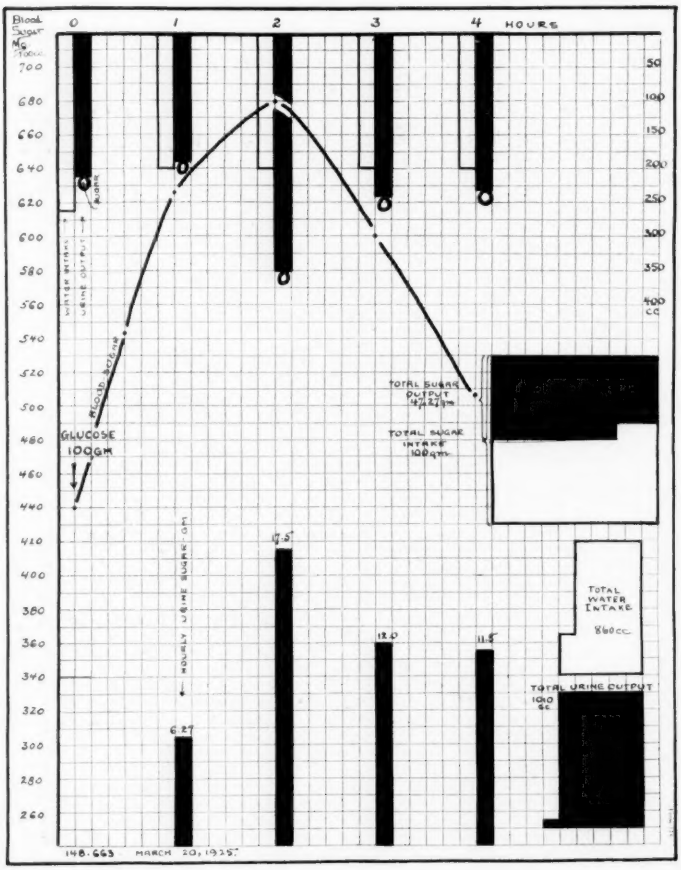

Fig. 5.—Glucose tolerance curve of patient with acromegaly associated with diabetes, showing high blood sugar content; examination revealed plasma chloride, 530 mg. per hundred cubic centimeters; blood urea, 51 mg.; blood uric acid, 2.7 mg.; blood creatinine, 1.6 mg.; blood nonprotein nitrogen, 55.1 mg., and plasma acetone, a trace.

not the acromegaly itself had been a causative factor in the production of the diabetes. The history of this patient emphasizes the fact that the diabetes that develops in a case of acromegaly does not differ from

any other case of diabetes. The patient improves just as readily under proper treatment and retrogresses as promptly with lack of treatment. Insulin seems to be just as effective in these cases as it is in others.

Another case of acromegaly has recently come under my observation, and since the carbohydrate metabolism has been investigated, it is included here, although as shown by the glucose tolerance test, in this case diabetes is not associated with the acromegaly.

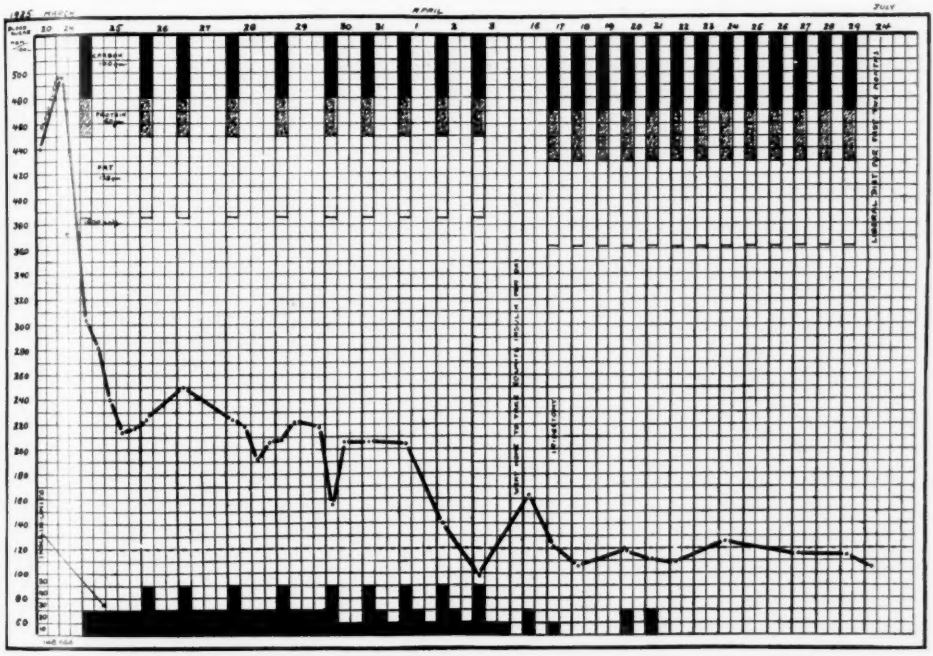

Fig. 6. Daily blood sugar level of patient whose glucose tolerance curves are given in Figures 5 and 7, showing apparent disappearance of diabetes.

CASE 3.—A woman, aged 43, had been perfectly well in early life, had married at the age of 24, and since marriage had had only one menstrual period. For ten years she had had extremely bronzed skin. In 1916 she had had an attack of "painful joints," so severe that morphine had been required to control the pain. In 1918 she had had an attack of influenza after which she had been in a weakened condition for two years. This was followed by a marked change in her features, and enlargement of the hands. The size of her shoes increased from 5½ to 8½; she used to wear a No. 7 glove, but at this time could not get a glove that would fit her. Between 1910 and 1915 she had gained 45 pounds (20.4 Kg.) in weight (Fig. 9). In 1921 she had three attacks of renal colic and passed a stone. She complained of extreme thirst, to relieve which she drank large quantities of water.

Urinary examination showed no glycosuria. A roentgenogram showed an enlarged sella turcica. There was a change in the field of vision as indicated on the chart (Fig. 10), with marked dimness of vision. She complained of marked headaches and of nocturia. The jaws were markedly prognathous; the teeth were spread, the nose and lips were abnormally large, and there was a marked growth of hair on the legs. The thyroid was not enlarged.

Although some of the symptoms in this case suggest diabetes, the presence of that condition was ruled out by the glucose tolerance test, although there was slight leaning toward impairment of carbohydrate tolerance (Fig. 11).

In spite of the points emphasized by Cases 1 and 2, and of the lack of evidence of diabetes in Case 3, the striking frequency with which diabetes occurs in cases of acromegaly cannot be disregarded. Is it not possible that the factor that causes enlargement and hypersecretion

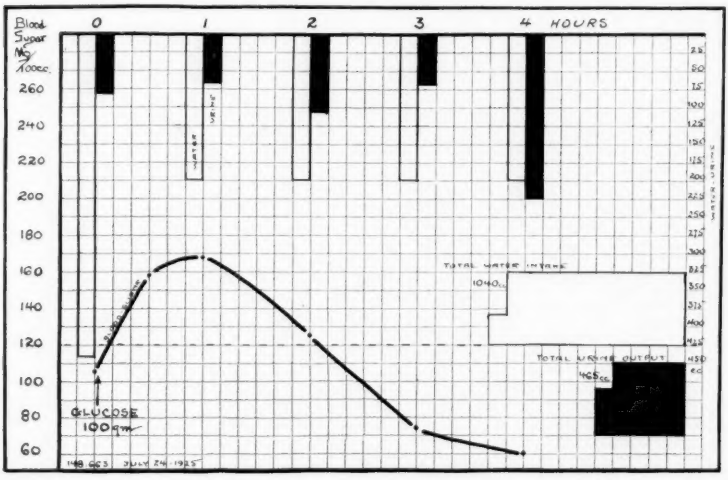

Fig. 7.—Normal glucose tolerance curve of patient whose curve is given in Figure 5, showing apparent disappearance of diabetes; examination revealed plasma chloride, 585 mg. per hundred cubic centimeters; blood urea, 21 mg.; blood uric acid, 1.9 mg.; blood creatinine, 1.1 mg.; nonprotein nitrogen, 25.7 mg., and plasma acetone, negative.

of the posterior part of the pituitary gland may also cause the disturbance of the insulogenic function of the pancreas? If the pituitary gland were primarily concerned in the production of diabetes, then such cases as those cited above should not respond to the ordinary treatment as readily as other cases, but such has not been our experience. Moreover, removal of the pituitary gland ought to cure diabetes in such cases, but unfortunately it does not. The occasional report of an improvement of the diabetic condition in these patients must be regarded with caution, for one encounters many atypical cases of diabetes as well as acromegalic diabetes such as von Noorden reports in his series. Such cases as

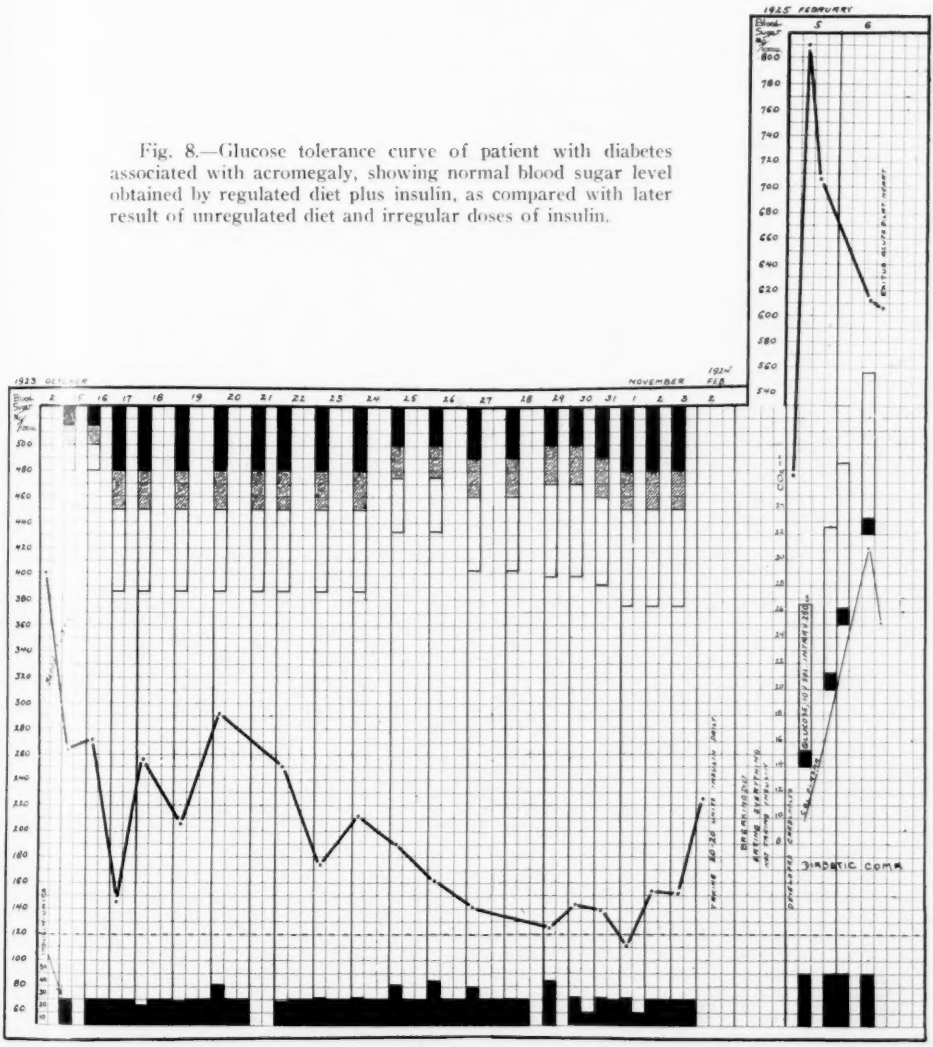

Fig. 8.—Glucose tolerance curve of patient with diabetes associated with acromegaly, showing normal blood sugar level obtained by regulated diet plus insulin, as compared with later result of unregulated diet and irregular doses of insulin.

these reported here therefore only emphasize the complexity of this problem.

REVIEW OF THE LITERATURE

In order to investigate the studies in this field, the literature has been searched and the following abstracts are offered as epitomizing all that I have been able to find regarding this subject.

Chauffard,[1] in a clinical lecture on pituitary diabetes, reviews the general facts regarding this relationship. He states that the relationship between pituitary disturbance and diabetes insipidus is common, the first case recorded

Fig. 9.—Patient with acromegaly with suspected associated diabetes, showing acromegalic development of face and hands.

having been reported by an Italian, Farini. As for the correlationship of acromegaly and diabetes mellitus, he asserts that the first case of this kind was observed in his clinic in 1899-1900, and reported by Ravaut. The patient was a woman, aged 29, who at 21 had developed acromegaly with cessation of menstruation. Pituitary extract was administered without any result. The disease progressed during the next five years, and she became obese, her weight increasing to 83 Kg. (182.6 pounds). At this time severe headaches developed, left visual disturbance, great thirst, polyuria, pruritus vulvae and a loss of 19 Kg. (41.8 pounds) in weight. She was several times on the verge of coma, the condition yielding to massive alkalinization, but she soon succumbed to pneumonia.

1. Chauffard: Pituitary Diabetes, M. Press, London, **110**:142, 1920.

Postmortem examination revealed a fungating tumor the size of a walnut situated in the pituitary gland and adherent to the sella turcica. A histologic examination of the gland showed it to be an adenoma with sarcomatous elements, a type of tumor that is supposed to increase the function of the gland, causing hyperpituitarism. The medulla and fourth ventricle were healthy. All the other organs were hypertrophied, including the pancreas, which weighed 90 Gm. The heart was hypertrophied; the liver weighed 2.8 Kg., the spleen 200 Gm., the kidney 320 Gm. The small intestine measured 10.1 meters, the appendix 13 cm. "As the patient's growth had come to an end, and she could not develop into a giant, the developmental energy had been concentrated on the viscera," says the author.

Of especial importance is the recent exhaustive article by Sachs and Macdonald,[2] who state that in accordance with their views in regard to glycosuria, the various investigators in this field may be divided into three groups: "First, those who assume a center in the neighborhood of the hypophysis, as claimed by

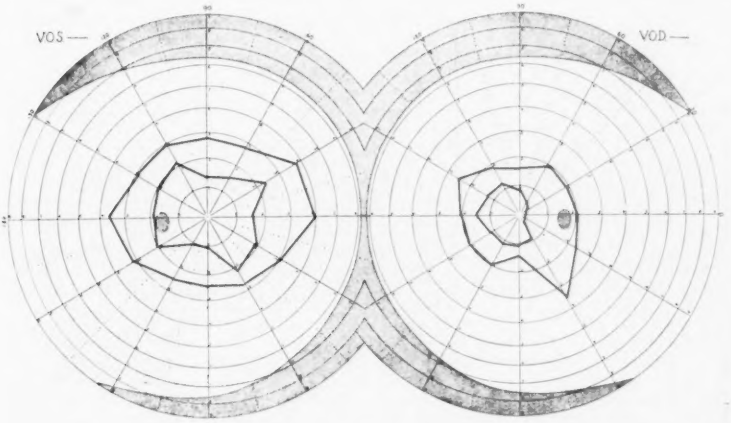

Fig. 10.—Change in field of vision in patient shown in Figure 8.

Rath, Loeb and more recently by Aschner. Second, those who think that the glycosuria is due to secondary changes in the other ductless glands, notably the pancreas—Pineles, Hausemann and Dallemange—who found atrophic changes in the pancreas, and Lorand who assumes that the sugar is the result of changes in the thyroid due to an interrelation with the hypophysis. Third, those who hold that the glycosuria is directly due to the increased production of some substance in the pituitary gland which is the active agent in producing the condition," notably Naunyn, Borchardt, Bernstein and Falta.

They cite the findings reported by Houssay, Hug and Malamud that there is no marked difference in carbohydrate metabolism in dogs after the pituitary gland has been removed. Sachs and MacDonald state that their studies of glucose tolerance and of the response to insulin show that diabetes in cases of pituitary dysfunction is similar to diabetes in those cases in which the primary cause is a lesion in the pancreas. They cite a case reported by Blum and Schwab[3] in which

2. Sachs, E., and MacDonald, M. E.: Blood Sugar Studies in Experimental Pituitary and Hypothalamic Lesions (with bibliography), Arch. Neurol. & Psychiat. **13**:335-368 (March) 1925.

3. Blum, L., and Schwab, H.: Diabète acromegalique et insuline, Compt. rend. Soc. de biol. **89**:195, 1923.

the hyperglycemia responded to insulin treatment but on the other hand they also cite the report by Burn that when insulin is injected simultaneously with an injection of the posterior lobe of the pituitary, the usual hypoglycemia is prevented. This appears to be in accord with the conclusion of Olmstead and Logan "that there is an antagonistic action between the insulin and the pituitary secretion as shown by experiments on decerebrated cats."

In animals used in the experimental studies by Sachs and MacDonald, when the posterior lobe was absent or there was a hypothalamic injury there was a delayed rise in the sugar tolerance curve, while when only the anterior lobe had been removed, the sugar tolerance curve was of the normal type. The authors think that their work has shown quite conclusively that the pituitary gland is not essential to life, a view first expressed by Victor Horsley.

They cite the work of Aschner, who revived the hypothesis of Erdheim that a disturbance of the centers of the hypothalamus is the essential cause of

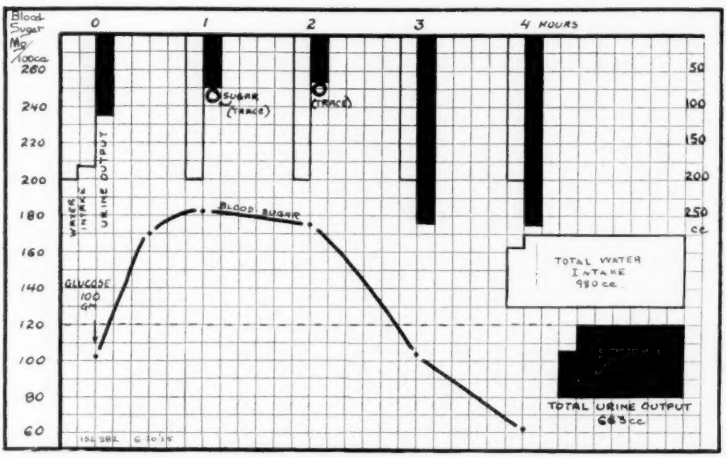

Fig. 11.—Glucose tolerance curve of patient with acromegaly with suspected association of diabetes, showing practically normal blood sugar level; examination revealed plasma chloride, 495 mg. per hundred cubic centimeters; blood urea, 45 mg.; blood uric acid, 2.6 mg.; blood creatinine, 1.3 mg.; blood nonprotein nitrogen, 51.3 mg., and plasma acetone, negative.

many symptoms attributed to the hypophysis; of Sweet and Allen who after twenty-two total hypophysectomies by the temporal route, concluded "that the gland can be removed without danger to life"; and of Brown who observed no untoward symptoms after the gland was completely removed from dogs, two of his dogs being alive, one two years and one nine months after the operation. Sweet and Allen and Brown made careful histologic studies of the removed glands. Sachs and MacDonald also cite the extensive work of Camus and Roussy,[4] who maintain that the pituitary gland is not necessary for life. These investigators think that most deaths after a hypophysectomy are due to injury of the hypothalamus, meningitis or hemorrhage and that polyuria is due to lesions of the tuber cinereum.

4. Camus, J., and Roussy, G.: Experimental Researches on the Pituitary Body, Endocrinology **4**:507-522 (Oct.-Dec.) 1920.

Various authors report that polyuria may be checked by lumbar puncture. Sachs and Macdonald also refer to the work of Camus, Gournay and LeGrand, who state that a lesion of the tuber cinereum in rabbits produces glycosuria which lasts for several months. These authors cite the work of Keeton and Becht, who found hyperglycemia following hypophysectomy.

The authors offer the following conclusions:

1. Complete removal of the pituitary gland does not lead to the death of the animal if the hypothalamus is not injured.

2. Their experiments confirm the conclusions of others that polyuria is apparently due to hypothalamic injury.

3. The average blood sugar level in fasting animals is slightly lower after pituitary or hypothalamic operation, but this level may be within the normal limits of variation.

4. Although transient glycosuria and hyperglycemia for from one to two days occurred after hypothalamic puncture in a few cases, they do not consider this of great importance.

5. They were unable to produce a permanent glycosuria experimentally, although it has been observed in cases of pituitary disease, some of which, though not all, were due to hyperfunction of the anterior lobe, which cannot be produced experimentally.

6. In all cases except those in which the anterior lobe had been removed, the maximum height of the blood sugar curve was reached at the end of one hour in contrast to the curve in normal animals in which the maximum height occurs at the end of one-half hour.

7. The blood sugar curve in the cases in which the anterior lobe had been removed was of the normal type.

Goetsch, Cushing and Jacobson (reported by Ellis [5]) have demonstrated the "occurrence of glycosuria after handling and electrical stimulation of the pituitary body, and of an increased carbohydrate tolerance in animals after hypophysectomy," thus supporting "the theory developed from clinical observations that both acromegaly and glycosuria result from overactivity of the hypophysis."

Froment (reported by Ellis) was unable to find any case in which glycosuria was associated with hypophyseal tumors in the absence of acromegaly, while, on the other hand, Anders and Jameson [6] compiled a number of cases of lesions of the pituitary body in which glycosuria was present although there was no acromegaly. Ellis states, however, that a careful analysis of their data shows that in the majority of cases the "glycosuria was transient or terminal, and associated with either marked intracranial pressure or injury to the base of the brain."

In an experimental study of the effects of the hypodermic injection of hypophyseal extract, Claude and Baudouin [7] found that a varying degree of glycosuria was produced, the most marked glycosuria being obtained in cases of arthritis and in a prediabetic condition. The maximum degree of glycosuria was obtained when the extract was injected before a meal, while the response was feeble when the meal was taken from one-half to one hour or more before the injection. When the meal was taken from two and one-half to three hours before the injection, the degree of glycosuria was very slight. The authors

5. Ellis, A. W. M., and Trumbull, H. M.: Hyperglycemia and Glycosuria in Acromegaly, Lancet **1**:1200-1203 (June 14) 1924.

6. Anders, J. M., and Jameson, H. L.: The Relation of Glycosuria to Pituitary Disease and the Report of a Case with Statistics (with bibliography), Am. J. M. Sc. **148**:323-329, 1914.

7. Claude, H., and Baudouin, A.: Le mécanisme de la glycosurie hypophysaire, Compt. rend. Soc. de biol. **73**:568-570, 1912.

explain this phenomenon by the statement that the glycosuria is due to some type of liver insufficiency as the result of which the glucose is not transformed into glycogen, for, as they state, were the injection of the extract to bring about the mobilization of sugar in the blood it should be equally effective regardless of meals.

From experiments on rabbits, Borchardt[8] found that the injection of hypophyseal extract produced glycosuria and in his last two cases hyperglycemia also was produced. He searched the literature to find how many cases in which diabetes was associated with acromegaly had been reported in the hope of ascertaining whether the glycosuria found in acromegaly is due to a hyperfunction or hypofunction of the hypophysis. He compiled from the literature 176 cases of acromegaly among which diabetes was present in 35.5 per cent. In eight other cases a limited degree of glycosuria had been reported. Altogether there were seventy-one cases, or 40.32 per cent, which showed a pathologic weakness of the carbohydrate metabolism. The degree of impairment varied from slight alimentary glycosuria to coma. In 1897 Strümpell[9] described a case in which the glycosuria disappeared entirely in spite of the large carbohydrate intake, and later reappeared without any apparent reason, again disappearing shortly before death; and von Noorden[10] says that of his four cases of acromegaly-diabetes, only two followed a normal course, the two other cases showing fluctuations of the glycosuria which were entirely independent of the food intake and indicated the influence of some other undiscovered factors.

Borchardt,[11] in another article, cites the work of Hausemann and Dallemagne, who found in the majority of their cases that the pancreas was histologically normal, and of Benda,[12] who described a case of acromegaly with involvement of the pancreas but without diabetes.

Borchardt makes an observation that has been verified by numerous authors, that in all acromegaly-diabetes cases there was a hypoplastic tumor of the hypophysis, while in acromegaly without diabetes the hypophysis had often degenerated, which certainly strongly suggests a relationship between hyperfunction of the hypophysis and diabetes. The author endeavored to prove this by the injection of hypophyseal extract in rabbits, thus producing both glycosuria and hyperglycemia. He thinks that one should be cautious in deciding whether or not diabetes is always latent in acromegaly and also whether or not it is ever completely cured, as in many of the cases cited, there was but a single urinary examination. Glycosuria is more frequently found in acromegaly than in any other disease. In most of the reported cases, however, the pathologic examination did not reveal any involvement of the pancreas.

Borchardt concludes that the simplest explanation for diabetes in association with acromegaly it that it is due to an increased secretion of the hypophysis; as the hypophyseal tumor degenerates this secretion ceases, and may bring about cessation of the diabetes.[13]

It appears that the majority of authors accept the theory advocated by Loeb in 1898, that diabetes in acromegaly is due to pressure of the hypophyseal tumor on a hypothetical sugar centrum in the brain, the seat of which he

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8. Borchardt, L.: Experimentelles über den Diabetes bei der Akromegalie, Deutsch. med. Wchnschr. **34**:946, 1908.

9. Strümpell, A.: Ein Beitrag zur Pathologie und pathologischen Anatomie der Akromegalie, Deutsch. Ztschr. f. Nervenh. **11**:51-87, 1897.

10. Von Noorden, C.: Die Zuckerkrankeit und ihre Behandlung, Berlin, 1910.

11. Borchardt, L.: Die Hypophysenglykosurie und ihre Beziehung zum Diabetes bei der Akromegalie, Ztschr. f. klin. Med. **66**:332-348, 1908.

12. Benda, C.: Beiträge zur normalen und pathologischen Histologie der menschlichen Hypophysis cerebri, Berl. klin. Wchnschr. **37**:1205, 1900.

13. The table accompanying Borchardt's article includes a complete summary of the cases of diabetes associated with acromegaly.

placed in the region of the tuber cinereum. This theory, however, does not explain why, in certain cases of hypophyseal tumor without acromegaly, no diabetes occurs. Many authors cite the experience that in all cases of acromegaly complicated with diabetes there is a hyperplastic tumor of the hypophysis, whereas in cases of acromegaly without diabetes one often finds degeneration of the hypophysis, which points to the interdependence of hyperfunction of hypophysis and diabetes; this is in full harmony with the pathologic-anatomic findings. Cases of acromegaly investigated by Benda show a transition of hyperplasia of the hypophysis to adenoma and finally to sarcoma. This would explain why diabetes in acromegaly so often disappears later, as soon as the increased production of the hypophyseal secretion has ceased.

Kollarits[14] reported fifty-one cases of hypophyseal tumors without acromegaly, not one of which developed diabetes. Such a varying relationship of hypophyseal tumors to acromegaly does not seem to be in harmony with Loeb's theory.

Lorand[15] advanced another theory in which he suggests that diabetes in cases of acromegaly is due to an increased function of the thyroid and its influence on the pancreas. From the fact that thyroid changes are often present in acromegaly, Lorand concludes that they precede and perhaps cause the changes in the hypophysis.

Camus and Roussy,[4] in their experimental researches on the pituitary body in dogs, found that the occurrence of polyuria after hypophysectomy depended on whether or not the base of the brain had been injured. To verify this finding they injured the base of the brain without injuring the hypophysis and a marked polyuria resulted. They found that the protraction of polyuria from this cause varied, lasting from a short time to many months. Glycosuria followed in one dog in which the polyuria had persisted for seven months. The administrations of pituitary extracts were ineffectual. The optopeduncular region which lies at the level of the tuber cinereum in the vicinity of the infundibulum was the only zone within which a lesion was followed by polyuria.

These authors conclude: (1) that neither the partial removal of one or of both lobes nor total removal of the pituitary body either modifies appreciably the tolerance to carbohydrates or causes the appearance of alimentary glycosuria; and (2) "that the injections of concentrated extracts of the posterior lobe, of the anterior lobe or of the whole hypophysis, do not sensibly modify — in the animals operated on — the limit of tolerance to carbohydrates," after the operative procedures described in the foregoing.

An interesting instance of the occurrence of hyperglycemia and glycosuria in a case of acromegaly has recently been reported by Ellis.[5] The facts of the case are briefly these: A woman, aged 42, had a blood sugar of 430 mg. per hundred cubic centimeters, and heavy acetonemia. On three days fasting she became sugar free. Her diet was gradually raised to 83 Gm. of carbohydrate, 44 Gm. of protein, 76 Gm. of fats, a total of 1,200 calories — a very low diet — and a hypophysectomy was performed, two, five and fifteen months after which the blood sugar was, respectively, 150, 120 and 130 mg. per hundred cubic centimeters. Two and three years later glucose tolerance tests gave the following results: (a) blood sugar before ingestion of 50 Gm. of glucose, 147 mg. per hundred cubic centimeters; three-quarters of an hour after, 270 mg. per hundred cubic centimeters; two hours after, 220 mg. per hundred cubic centimeters; (b) blood sugar before ingestion of 50 Gm. of glucose, 180 mg. per hundred cubic centimeters; three-quarters of an hour after, 220 mg. per hundred cubic centimeters, and two hours after, 230 mg. per hundred cubic centimeters.

14. Kollarits, J.: Hypophysistumoren ohne Akromegalie, Deutsch. Ztschr. f. Nervenh. **28**:88-105, 1905.

15. Lorand, A.: Pathogénie du diabete dans l'acromègalie, Compt. rend. Soc. de biol. **56**:554, 1904.

The author does not consider this as a case of diabetes, but rather as a disturbance of carbohydrate metabolism due to some obscure cause. To quote his words: "As will be seen by the case here reported, it (glycosuria) may, however, attain the proportions of a true diabetes, and in the literature can be found reports of cases showing all the symptoms and complications of that disease." "Though ketonuria is stated to be rare in acromegaly, Froment (J. Neurol. **29**:664, 1922) has been able to collect a dozen instances in the literature, in which death from typical diabetic coma has ensued . . . ." "It is generally stated, perhaps on somewhat meager evidence, that the glycosuria of acromegaly is singularly insusceptible to changes in diet; in our patient no support for this statement was found, the urine became sugar-free on fasting as rapidly as would be expected in a true diabetes of equal severity." "The relatively satisfactory carbohydrate metabolism following removal of the hypophysis, in the case described above, suggests that in this patient the glycosuria was not due to pancreatic deficiency," and he tries to explain the condition as being due to the fact that pituitary extract counteracts the action of insulin as shown by Burn in his work on rabbits.

If we analyze the data on this case reported by Ellis, I think that we can assume with a fair degree of accuracy that it was a case of diabetes, for we know that there is in certain cases an association of these two conditions, acromegaly and diabetes. Were one given the laboratory and clinical data by themselves, I think no one would hesitate for a moment to make a diagnosis of diabetes. The curves of the two glucose tolerance tests, done a year apart, closely simulate diabetic curves, although unfortunately the author stopped his observations at the end of the second hour, which is not a long enough period to furnish final information. Fasting produced a sugar free condition; it always does in a diabetic patient. A low diet for a time kept the sugar in check, as one would expect in a case of diabetes. Hypophysectomy was performed and the author attributes all the progress to this operation. I have serious doubts about this point since the patient was under a diabetic regimen. Moreover, later a progressive hyperglycemia developed; the fasting blood sugar in 1921 was 150-120 mg. per hundred cubic centimeters; in 1922, 130 mg.; in 1923, 150-140 mg., and in 1924, 180 mg., a progressively diminishing carbohydrate tolerance which, if it keeps on, is bound again to bring the patient into a severe diabetic condition, even though the pituitary gland has been removed. Diabetes is diabetes, whatever be the primary cause. That the pituitary gland may play some part in its causation, no one can deny; but we have still to prove that hypophysectomy will cure diabetes in the case of acromegaly.

Brooks[16] reports an interesting case of acromegaly in a man aged 30. The patient was an Englishman whose head was injured in 1891; he was in good health subsequently until 1896, when acromegaly became manifest. During the later year he was treated for syphilis which was supposed to be of recent

16. Brooks, H.: A Case of Acromegalie, with Autopsy, New York M. J. **65**:418-421, 1897.

origin. Two months before he was seen by the author he was treated unsuccessfully for syphilitic iritis. At this time he developed marked thirst, shortly afterward becoming drowsy and irritable. "He had attacks of dyspnea, some of long duration." Finally, one day after a short walk he went into a state of collapse, and the next morning was still in a stupor, although he could be aroused. His tongue was coated and dry; the skin was cyanotic; the pulse was feeble and rapid; the abdomen was distended and tympanitic; there was an acetone odor on the breath; the right pupil was dilated and did not react to light; the left pupil was normal; the temperature was normal. The urine contained 7.5 per cent sugar. The stupor gradually deepened, and he died the next morning.

The postmortem examination revealed a tumor of the hypophysis, an ovoid red mass, measuring 1.5 cm. from before backward and 0.7 cm. from above downward. It was attached below, apparently, to the pituitary body. The mass was of a soft jelly-like consistency, and was quite vascular. It was found to press directly on the left optic tract just posterior to the chiasm. The tumor was attached to the hypophysis, which was enlarged to about five times its volume. The pituitary fossa was greatly enlarged, and the bones making up its wall were abnormally thin. No adhesions existed between the pituitary body or the tumor and the surrounding tissues.

Hausemann, reported by Chadbourne,[17] thinks it is not unlikely that an intimate relation exists between acromegaly and diabetes, and although diabetes was stated to have been present in only twelve of the ninety-seven undoubted cases of acromegaly that he was able to find in the literature, these cases were those which had been most accurately observed.

Chadbourne reports the case of a man, aged 40, who at the age of 19 "began to have sick headaches every few weeks." These attacks became less frequent after he was 24 years old and had been absent during the last four years. When he was 25 years old his hands and jaw began to get larger. At the age of 36, his appetite increased markedly and he began to have great thirst and to pass large amounts of urine; these symptoms, together with itching of the skin, had persisted. During the last four years he had lost 79 pounds (35.8 Kg.) in weight. When seen by the author he complained of failing eyesight. The urine contained a large amount of sugar. At this time his weight was 211 pounds (95.7 Kg.); his height, 6 feet, 3 inches (190.5 cm.), and he had the typical acromegalic facies. The author says nothing about diabetic treatment but the description is significant.

Machwitz[18] reported a case of acromegaly-diabetes in a man aged 46. The acromegaly started when he was 22 years old, but the onset of diabetes dated back only two years. The patient had a heavy glycosuria not related to carbohydrate intake, but he had no acidosis. Roentgen-ray examination showed enlargement of the sella turcica, no bitemporal hemianopsia and only slight disturbance of vision. It is interesting to note that an 18 year old son of the patient also had acromegaly.

Lereboullet[19] has described a case, the circumstances of which appear to confirm the assumption that the alimentary glycosuria or diabetes sometimes associated with acromegaly is due to nerve irritation at the floor of the third ventricle, produced by enlargement of the sella turcica. The author believes that in contrast to diabetes insipidus, which is due to the pituitary gland itself, the glycosuria type of diabetes seems to be the result of irritation in the vicinity of the pituitary gland but not within the gland itself.

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17. Chadbourne, T. L.: A Case of Acromegaly with Diabetes, New York M. J. **67**:449, 1898.

18. Machwitz: Akromegalie, kombiniert mit Diabetes, München. med. Wchnschr. **67**:198, 1920.

19. Lereboullet, M.: Diabète et acromègalie, Progrès méd. **35**:106-108 (March 6) 1920; abstr., J. A. M. A. **74**:1356 (May 8) 1920.

Labbé and Langlois[20] report the case of a man, aged 48, who had hypertrophy of the pituitary gland with acromegaly and also presented symptoms of diabetes; but there was no diminution in weight and pituitary treatment did not affect the polyuria. "The glycosuria, however, was markedly influenced by pituitary treatment, plus reduction of the intake of carbohydrates, the sugar in the urine dropping from 129 mg. per hundred cubic centimeters to zero in four months." This case also seems to confirm the conclusion of the authors "that not the pituitary gland itself, but an irritation of some center in the base of the brain is responsible for the production of diabetes and polyuria."

Van Nüys[21] has reported a case of diabetes of four years' duration with a loss of 100 pounds (45.4 Kg.) in weight in a patient in whom the presence of hyperpituitarism was suggested because of her facies and the heavy glycosuria. She had "heavy cheek bones, a broad nose and undershot jaw." The breath had an acetone odor. "Repeated roentgenograms of the skull seemed to show a much enlarged sella turcica; the shadows, however, were obscure as if a growth partly obliterated the outlines of the region." He says that pituitary extract was given without appreciable effect. The Allen treatment for diabetes and potassium iodide were of benefit, and from a state of coma, because of which the author was first consulted, the patient improved until she was able to sit up and walk a little when she left the hospital.

Anders and Jameson[6] report the case of a woman, aged 46, weighing 170 pounds (77.1 Kg.), who had a large gangrenous ulcer in the palmar surface of the hand which extended slowly until death occurred. Throughout her illness she had polydipsia, polyuria and glycosuria, from 5 to 7 per cent. The glycosuria appeared two years after the onset of a typical acromegaly. She also had hyperthyroidism. She died in coma a month after she was first seen by the authors. They cite the statement by Dock that diabetes arising in the course of acromegaly is cerebral and due to the pituitary disease as is shown by the fact that "diabetes is most marked with the largest tumors."[22]

Grenet and Tanon[23] report a case of acromegaly with diabetes in a woman, aged 50. She had the typical acromegalic features, which had been developing over a period of seventeen years. The vision of the right eye was completely lost, and the left eye did not distinguish objects situated at the extreme left of the visual field. The eye examination revealed double optic atrophy, complete on the right, incomplete on the left; temporal hemianopsia of the left eye; external strabismus of the right eye; no paralysis of the ocular muscles. The urine showed a heavy glycosuria, and she had some diabetic symptoms. For several years she had had polydipsia, drinking from 2 to 3 liters of water daily. Her appetite was good but not exaggerated. The urine output was 3 liters a day. The glycosuria had apparently existed for the preceding seven months, as examination of the urine before that time had revealed no sugar. Under treatment the glycosuria decreased from 66 to 32.72 Gm. a liter.

This case is of interest because of the late appearance of the glycosuria though the acromegaly had been present for seventeen years.

Koopman[24] cites from the literature a number of cases of acromegaly in which the patients died in diabetic coma (Stricker, Bury, Stadelmann, Strümpell, Hinsdale, Ravaut, Dallemange, Umber).

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20. Labbé, M., and Langlois, S.: Acromègalie et diabète, Bull. et mém. Soc. méd. d. hôp. de Paris **43**:229-233 (March 7) 1919; abstr., J. A. M. A. **72**:1796 (June 14) 1919.

21. Van Nüys, F.: Case Report of Hyperpituitarism and Hyperglycemia, Boston M. & S. J. **181**:465-466 (Oct. 9) 1919.

22. This article is accompanied by an excellent table of reported cases of acromegaly with glycosuria compiled from the literature.

23. Grenet, H., and Tanon, L.: Acromègalie et diabète, Rev. Neurol. **15**:84-86, 1907.

24. Koopman, J.: Hypophysaire diabetes, Nederlandsch. Tijdschr. v. Geneesk. **2**:1071-1076 (Oct. 11) 1919.

He speaks of a remarkable case of diabetes with acromegaly described by Stricker in the Dutch literature. In this case marked lipemia was present and the urine contained a large amount of acetone and diacetic acid. Coma was expected, but the patient died of paralysis of the heart. "Generally," says Koopman, "the diabetes as it is seen in cases of acromegaly, is not absolutely identical with the diabetes we generally see. Lery thinks it better not to speak of diabetes in these cases, but to call it glycosuria. The complications frequently seen in diabetes mellitus, as furunculosis, pseudotabes and arthritis, occur also in these cases but not so often."

Koopman cites a case of syphilis of the pituitary gland described by Cushing which presented a typical clinical picture of diabetes mellitus. Koopman also reports two cases of his own, in one of which the glycosuria was relieved by treatment with hypophyseal extract; in the other the patient improved at first but later refused to diet and to take the hypophyseal extract and died in coma.

A striking feature in these cases was the low protein tolerance. The author thinks that, while it cannot be proved that the diabetes was of pituitary origin, yet that the hypophysis certainly played a prominent rôle in the production was proved by the fact that the patients responded so well to treatment with pituitary extract.

Blum and Schwab [3] have presented two cases which offer an interesting comparative study of diabetes with and without acromegaly. Both patients received

TABLE 2.—*Response of Two Patients of Blum and Schwab to Thirty Units of Insulin*

	Diabetes With Acromegaly			Diabetes Without Acromegaly		
	Blood Sugar,	Urine		Blood Sugar,	Urine	
Time	Mg. per 100 Cc.	Volume, Cc.	Glucose per Liter	Mg. per 100 Cc.	Volume, Cc.	Glucose per Liter
8:35 a. m.	301	...	...	325	...	...
9:00 (30 units of insulin administered)	...	720	3	...	780	21
11:00	180	430	...	244	290	13
1:30 p. m.	173	320	...	160	400	..
3:30	251	670	...	155	190	..

the same treatment except that the patient with acromegaly, who had an immense appetite, received potatoes during the noon meal. The response of each of these patients to the injection of 30 units of insulin is shown in Table 2.

The authors conclude that the presence of acromegaly does not affect the reaction to insulin.

Allen [25] reports the presence of acromegaly with marked glycosuria in a woman, aged 50. Thirst and weakness were of recent onset, within the preceding six months, while the acromegalic features began to develop ten years before. She was passing from 3,720 to 8,940 cc. of urine daily and excreting from 200 to 480 Gm. of sugar, the specific gravity being from 1.035 to 1.043.

Carnot, Rathery and Dumont [26] describe a case of diabetes in a woman with the typical acromegalic facies, in whom roentgen-ray examination showed destruction of bone about the sella turcica, with considerable enlargement of the gland. The patient, who was 58, had developed diabetes three years before, the onset being marked by a large appetite, thirst, loss of strength and large quantities of sugar in the urine. Later she developed severe headaches but there was no vomiting. Two months before diplopia had appeared. The

25. Allen, W.: Acromegaly with Marked Glycosuria, Glasgow M. J. **66**:166-169, 1906.

26. Carnot; Rathery, and Dumont, J.: Acromègalie; diabète; tumeur hypophysaire, Bull. et mém. Soc. méd. d. hôp. de Paris **35**:921-935, 1913.

menopause occurred at the age of 42. The patient suddenly developed a fever and died. At necropsy the sella turcica measured 0.032 by 0.025 cm., and the hypophysis was enormous, weighing 14 Gm. Microscopic examination did not reveal any normal hypophyseal structure. The pancreas weighed 100 Gm., and autodigestion had taken place, but the islands of Langerhans were visible and quite numerous.

Verger, Massias and Auriat[27] report a case of acromegaly in which the carbohydrate tolerance was exaggerated and there was no reaction to the extract of the posterior lobe of the hypophysis.

The patient was a woman, aged 36, who for thirteen years had had epileptic attacks and a modified acromegaly limited to impairment of sight and hirsutism, the feet and hands remaining normal. Roentgen-ray examination of the skull showed enlargement of the sella turcica. There was no adiposity, no change in stature, no polyuria and no glycosuria. She was able to tolerate from 100 to 300 Gm. of glucose a day without glycosuria. After injection of 0.2 Gm. of posterior lobe extract and absorption of the carbohydrate meal, no glycosuria followed, and there was no increase in the excretion of urine.

This was a complex case of bilobar dysfunction of the hypophysis, the dysfunction of the anterior lobe producing the acromegalic symptoms while the dysfunction of the posterior lobe produced exaggerated carbohydrate tolerance and was the cause of the absence of reaction to the injections of extract of that lobe.

Variations in the incidence of glycosuria in cases of acromegaly are described in the literature. Thus, in a case described by P. Marie (cited by Borchardt [8]), glycosuria was present only once while the patient was on a full diet, but it appeared when the diet was sugar free. This occurrence of glycosuria independently of the diet is noteworthy. As noted above, in 1897 Strümpell described a like case, in which glycosuria disappeared in spite of a diet rich in carbohydrates, and reappeared later without any apparent reason, disappearing again shortly before death. Such cases are far from rare. Two of the four diabetic-acromegalic cases cited by von Noorden followed a normal course. In two others glycosuria appeared and disappeared again, regardless of the diet.

CONCLUSIONS

The following conclusions are drawn from personal experience with the two cases here reported, in which diabetes was associated with acromegaly, and from a study of the literature.

1. In general, hypopituitarism is accompanied by an increased carbohydrate tolerance and hyperpituitarism by decreased tolerance, but this is not an absolute rule.

2. In the majority of cases of so-called diabetes associated with acromegaly that have been reported in the literature, especially in older cases, the diagnosis of diabetes was made on the basis of urine exami-

27. Verger, H.; Massias, C., and Auriat, G.: Exagération de la tolérance aux hydrates de carbone et absence de réaction à l'extrait de lobe posterieur de l'hypophyse chez une acromègalie, Compt. rend. Soc. de biol. **87**:197, 1922.

nation only. Since glycosuria does not always indicate diabetes, this should be borne in mind in evaluating these reports.

3. In most reported cases and in the two here reported, the onset of acromegaly preceded the onset of diabetes by many years.

4. The treatment of diabetes associated with acromegaly does not differ from the treatment of the ordinary case, and the response of the former type of case does not differ from that of the ordinary case.

5. Patients in whom diabetes is associated with acromegaly if not controlled are as subject to acidosis and coma as the ordinary case.

6. Hypersecretion of the posterior part of the pituitary gland seems to produce hyperglycemia and glycosuria. Whether this is the predisposing factor is not certainly established; the incidence of diabetes in acromegaly is rather high but, whatever the primary factor, the metabolic disturbance is due to a decreased insulogenic secretion. It may be that the factor that produces hyperpituitarism may also have some influence in producing the decreased insulogenic function which brings about diabetes.

7. Diabetes is always due to the same immediate factor, namely, a diminution of the insulogenic function and whether it is or is not associated with pituitary dysfunction, its course does not vary and the same treatment is indicated as in the ordinary case.

THE MECHANISM OF INSULIN ACTION *

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The discovery and isolation of the physiologically effective principle of the internal secretion of the pancreas by Banting and Best [1] in 1921 may be considered the culmination of the great amount of research work which received its impetus from the fundamental facts established by von Mehring and Minkowski in 1889.[2] At that time it was first found that pancreatectomy in dogs resulted in complete diabetes. Thirty-two years of research on carbohydrate metabolism and the problem of diabetes mellitus prepared the way for the important findings of Banting and Best which resulted in the isolation of insulin and its application as a therapeutic agent. The work of von Mehring and Minkowski was the first contribution of value toward a solution of the question of the etiology of diabetes mellitus. Through the work of Banting and Best it is now known that the pancreas secretes a hormone which is essential to normal carbohydrate metabolism, which can be extracted from pancreatic tissues, and which is physiologically effective when administered parenterally. It has also been shown that insulin in the presence of extracts from certain body tissues, such as muscle and liver, aids in the fragmentation of the sugar molecule. Yet the actual mechanism of insulin action, the chemical structure of the hormone, and the reactions in which it plays such an important rôle are unknown. It is conceivable that if this mechanism were discovered the knowledge gained might prove a powerful illuminant in the still shrouded question of the etiology of diabetes mellitus. In other words, if we knew how insulin acts in reestablishing the diabetic body's potential toward a normal carbohydrate metabolism we might be able to discover the missing pathologic link between the picture as represented by a totally depancreatized dog and by a human being with severe diabetes.

I

The experimental and clinical work on the nature of insulin action reported in this article was suggested by the observation that the effect of insulin in the animal body differed materially according to the method

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1. Banting, F. G.; Best, C. H., and MacLeod, J. J. R.: Am. J. Physiol. **62**:162 (Sept.) 1922; ibid. **62**:275, 1922; Proc. Am. Physiol. Soc., 1925.

2. Von Mehring and Minkowski: Centralbl. f. klin. Med., 1889, p. 339; Arch. f. exper. Path. u. Pharmakol. **26**:371, 1899.

of administration.[3] If insulin is injected subcutaneously in healthy rabbits in quantities of 1 unit per kilogram of body weight the blood sugar is lowered after about one hour to about 50 per cent. of the initial value. This level is maintained over a period of from one to two hours. The blood sugar then increases rapidly until at the fourth hour after the injection the normal level is again reached. These observations were first made by Banting and Best and later by MacLeod and others.

Insulin (1 unit per kilogram of body weight) administered *intradermally* in rabbits was found to have a greater blood sugar lowering effect than the same dose given subcutaneously to the same animal under identical conditions. With intradermal administration the level reached at the second hour after the injection is usually lower and remains low up to the fourth hour, and at the sixth hour the blood sugar level is still below the initial value. The same difference in reaction occurs when the insulin is used in the concentration of one-half unit per kilogram of body weight (Chart 1).

II

In the animal tests the difference between the two methods of administration consists of a more prolonged effect of the intradermally injected insulin. The difference in time of absorption of the injected insulin in different body tissues cannot be used as an explanation of the prolonged effect observed in these experiments. This is confirmed by the results in human beings, especially in diabetic patients, in whom the intradermal injection with definitely prolonged absorption of the insulin depot and the definitely later entrance of the insulin into the circulation is followed by a more rapid and more intensive effect. This more rapid and greater effect of the intradermally administered insulin in human beings was demonstrated by shortening the observation intervals used in the animal experiments to one hour and, in six cases, to twenty minutes.

Two experiments on the same subject, in which like doses of insulin from the same ampule and under the same dietary conditions were employed but in which the mode of administration of the insulin differed, constitute a series and are so referred to in the comment. It is shown that in 86 per cent. of the hourly series the intradermal injection is more effective at the first hour following the injection than the subcutaneous injection. In the twenty minute series there is a definite effect at the first interval (twenty minutes) following the injection made intradermally and none at this interval following the subcutaneous injection, as shown in the composite curve of six series (Chart 2). The more rapid onset of the blood sugar lowering effect

3. Müller, E. F., and Corbitt, H. B.: J. Lab. & Clin. Med. **9**:608 (June) 1924; **10**:695 (June) 1925.

of the intradermal injection cannot be due to a quicker absorption and entrance of the hormone into the circulation, as in that case the effect should disappear sooner than the effect following a subcutaneous injection, whereas the opposite is the fact. At the fourth hour 67 per cent of the intradermal injections had a greater blood sugar lowering effect than the subcutaneously introduced insulin under the same conditions and on the same subjects.

III

Since attempted intradermal injections of insulin in the human being were reported to be followed by necrosis of the skin we investigated the nature of the histologic changes in the skin and subdermal tissues following the intradermal and subcutaneous injections of insulin in animal experiments. The results showed that edema occurs in the area of the injection and that the vessel walls in this area show degenerative changes. The walls were found to be partially destroyed; thrombi were

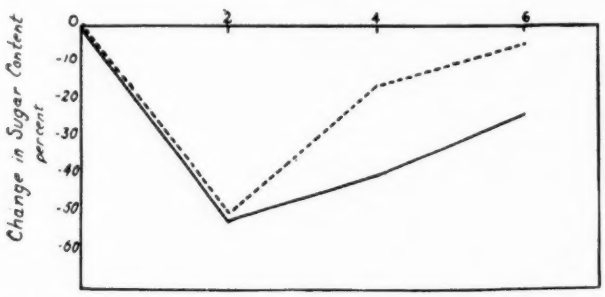

Chart 1.—Comparative effects of intradermal and subcutaneous injections of insulin in rabbits in twenty-one experiments; solid line: intradermal injections, eleven experiments; broken line: subcutaneous injections, ten experimnets.

present, some of which completely closed the vessels, others only partly blocked them. A certain amount of round cell infiltration was found. However, these changes in the injected area concern so small a region that the reported necrosis could not have been due to them.[4]

Tests on human beings have shown that the intradermal injection of commercial insulin has no deleterious effect on the skin. In the course of the experiments about 100 intradermal injections of insulin (Insulin-Lilly) have been administered to nondiabetic as well as to diabetic patients. In no case was the slightest reaction or damage to the skin noticed, either immediately or later, with the exception of slight and probably temporary pigmentation that was observed at the site of the

4. Müller, E. F., and Myers, C. N.: Proc. Soc. Exper. Biol. & Med. **22**:92, 1924.

injection. One patient, a girl, aged 12 years, with severe diabetes mellitus, was treated under our direction while in the Roosevelt Hospital (courtesy of Dr. Evan M. Evans). Over a period of twenty-two days she was given forty-four intradermal injections of insulin, from one to three injections daily, the average daily dose amounting to 28 units. As

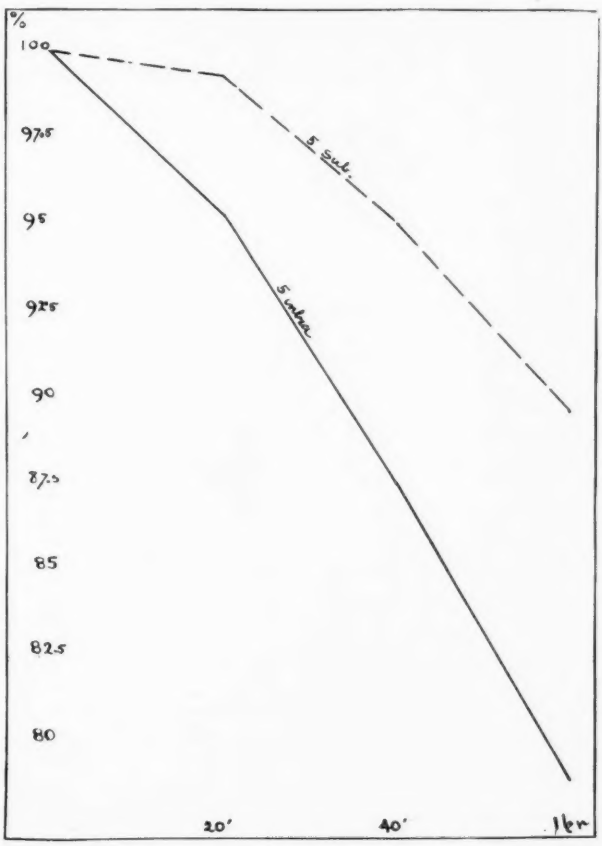

Chart 2.—Composite curves of six series showing effect on blood sugar level of subcutaneous and intradermal insulin injections (Table 3).

much as 14 units of the U-40 strength (0.35 cc.) was readily administered in a single wheal. Extensor surfaces of the forearms and thighs were used. Six weeks after the date of the last intradermal injection a few faintly pigmented spots were to be found on the forearms at the sites of some of the intradermal injections.

In all the tests the same lot number of insulin of the U-40 strength was used and insulin from the same ampule was employed for the various tests on the same individual. From 5 to 20 units could be administered intradermally in from one to three wheals. The procedure was as follows: A small fold of the skin of the extensor surface of the forearm was raised without pressure, cleansed with alcohol and a hypodermic needle introduced into the skin parallel to the surface. The needle and syringe must be washed with distilled water followed by dry sterilization. Any other method, especially sterilization by boiling in tap water must be avoided. If the wheal is administered correctly a white elevation remains visible for about ten minutes; after this the

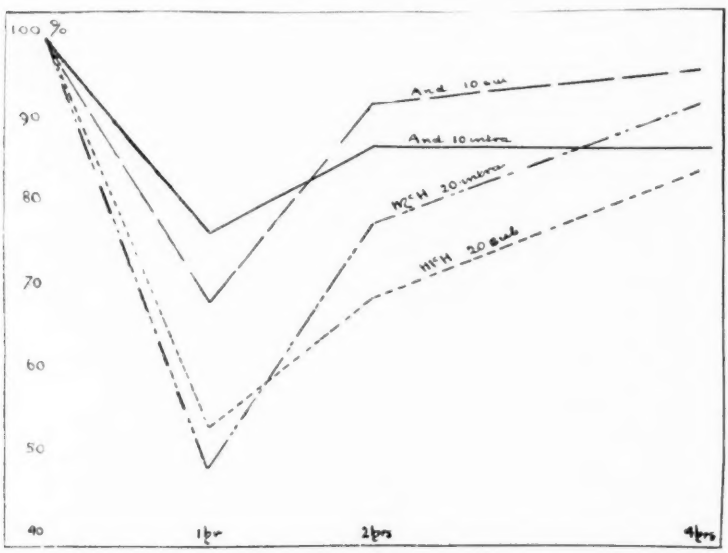

Chart 3.—Effect on blood sugar level in nondiabetic patients of subcutaneous and intradermal insulin injections.

margins become red and slight edema occurs in the surrounding area, but the center remains quite white for about fifty minutes. Later, the entire wheal again becomes white. The area of the wheal increased markedly in a large number of cases but remained sharply distinguished from the surrounding tissues. In hypersensitive cases the wheal at the later stage is not sharply distinguished from the other skin but is twice as large as the first visible wheal, and its white center and red margins remain visible for hours. In a few cases this increase in size does not take place but the wheal remains visible for from three to four hours, thus differing from a wheal induced by injection of a nonspecific protein.

Through the strong counterpressure of the skin small amounts of insulin may occasionally escape from the wheal after the needle is withdrawn. Experiments in which this occurred or in which slight bleeding occurred have been excluded.

Proof of a proper intradermal technic consists in (1) the evidence of a strong counterpressure against the advancing piston of the syringe, and (2) the immediate appearance of depressions of the hair follicles. In a few cases a slight pigmentation at the site of the injection was noticed subsequently but in no case was necrosis or clinical inflammation observed.

IV

Irrespective of the condition of the subject or of his carbohydrate metabolism at the time, it has been shown that under conditions as nearly constant as possible the two methods of administration differ in their effect on the blood sugar level. The blood sugar level of a nondiabetic subject in a morning fasting condition does not change materially during an observation period of from four to six hours. If one injects a nondiabetic subject with insulin the difference in the blood sugar lowering effect between the intradermal and the subcutaneous injection is small and not uniform. However, one feature in common is the quick recovery to the normal blood sugar level, even when large doses of insulin are used (Chart 3). The difference in response to the two methods at the first hour is slight, except for the smallest dose. The deepest point of the blood sugar curve is obtained during the first hour after both methods of injection. Rapid recovery to normal follows this first blood sugar lowering effect. In these tests the difference between intradermal and subcutaneous injections is greater with small amounts of insulin (5 units). This was also found to be the case when healthy animals were used in similar experiments. The effect of the intradermal injections in human beings with normal carbohydrate metabolism is more prolonged after the injection of small doses. With larger doses the subcutaneous injection has the more prolonged effect.

V

In patients with diabetes mellitus of varying degrees of severity the difference in reaction of the blood sugar level to the two methods of administration is more marked than in nondiabetic subjects (Table 2). However, this difference as between one case and another was not found to be a measure of the clinical severity of the disease. In other words, a clinically mild case might show a greater difference in the blood sugar level at one hour following the two methods of administration than a case clinically of greater severity. One feature of the curve did, however, run parallel to the clinical severity of the cases examined; namely,

the rapidity of the return of the blood sugar toward its original level. It is possible, however, that the difference in the reaction of the individual patient with diabetes mellitus to the two methods of administration may prove a new basis for a revised clinical classification of the disease. A study of the reaction of the individual case to such tests might conceivably have a bearing on prognosis and treatment.

For purposes of discussion we have divided the clinical material used in these tests into four groups, all showing glucosuria, as follows:

A. *Very Mild Glycosuria (Diabetes?).*—In this group were three cases (Cases 1, 2 and 3) of glycosuria without other symptoms of diabetes mellitus; the patients were men, aged 43, 50 and 54. The

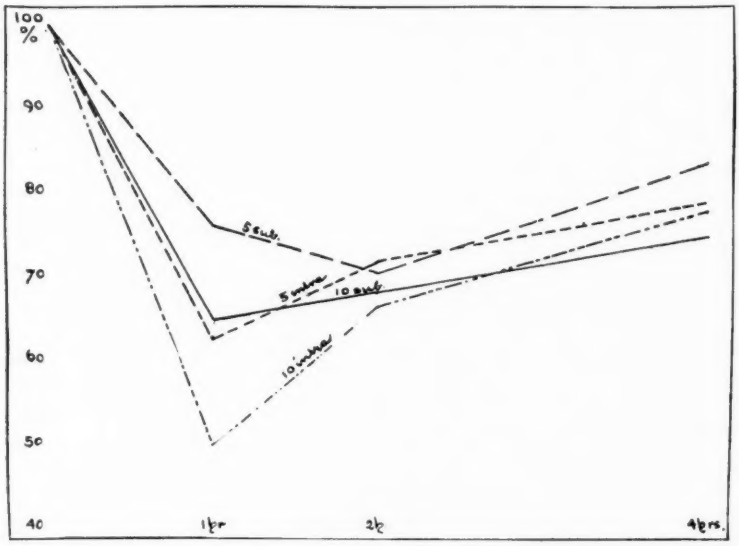

Chart 4.—Effect on blood sugar level in a case of mild glycosuria of subcutaneous and intradermal insulin injections.

original blood sugars were 182, 123 and 129 mg. per cent, respectively. The tests in these cases all followed a similar course and are represented by the curve of Patient 3 (Chart 4). It may be seen that there is a sharp recovery toward the normal level of the blood sugar with the intradermal administration following the drop registered in the first hour. The decline in the blood sugar after the subcutaneous injection continues into the second hour, showing a more prolonged but not as strong a hypoglycemic effect as the intradermal injection. At the first hour the average blood sugar lowering effect in these three cases for the 5 unit doses was 80 per cent of the initial blood sugar following

the subcutaneous injection and 60 per cent of the initial blood sugar for the intradermal injection. The 10 unit doses showed a similar relationship.

B. *Mild Diabetes Mellitus.*—In this group were three cases: Patient 4, a woman, aged 39, had an original blood sugar of 195 mg. per cent and 1.5 per cent sugar in the urine. Glycosuria had been first found thirteen months previously; she had pruritus and polyuria. Patient 6, a woman, aged 43, had an original blood sugar of 260 mg. per cent and urine sugar 1 per cent. Glycosuria had been first found four months previously; she had pruritus and had lost weight. Patient 5, a man, aged 65, had an original blood sugar of 204 mg. per cent and urine sugar 1 per cent. The sugar had been first discovered fourteen years previously; he had furunculosis, polyuria and polydipsia, and had lost weight. The urines were sugar-free on an average total available intake of 85 Gm. of carbohydrate and 60 Gm. of protein. In this group of cases there was also a definite similarity of architecture in the curves resulting from the tests. The curve of Case 5 is typical (Chart 5).

C. *Moderately Severe Diabetes Mellitus (Insulin Treatment).*—In this group were six cases: Patient 11, a woman, aged 22, had an original blood sugar of 240 mg. per cent and urine sugar of 1.6 per cent. Glycosuria had been first discovered two years and nine months previously; she had pruritus, had lost weight and suffered from nervousness and weakness. The urine was sugar-free on 38 Gm. of carbohydrate, 61 Gm. of protein and 175 Gm. of fat. Carbohydrate tolerance was sensitive to slight infections and nervous and emotional strains. Insulin treatment had been started twelve months previously, and the dose had been increased from 5 units twice a day to 10 units twice a day.

Patient 12, a colored man, aged 31, had an original blood sugar of 350 mg. per cent and urine sugar 2 per cent. Glycosuria had been first discovered fourteen months previously; he had polyuria and polydipsia, had lost weight and suffered from weakness. He developed pulmonary tuberculosis while under observation. The urine was sugar-free before the tuberculous infection on 108 Gm. of carbohydrate, 40 Gm. of protein and 204 Gm. of fat; after the tuberculous infection on 40 Gm. of carbohydrate, 54 Gm. of protein and 185 Gm. of fat. Insulin treatment was begun at the time of the tests, the dose being 10 units twice a day.

Patient 10, a colored man, aged 43, had an original blood sugar of 278 mg. per cent and urine sugar 4 per cent. Glycosuria had been first discovered six months previously; he had moderate polyuria and polydipsia, and had lost weight. The Wassermann reaction was + + + + (asymptomatic ? syphilis). The urine was never sugar-free without insulin. The patient was known to make untruthful reports as to his food intake. The insulin treatment had been started two months previously, the dose being 10 units twice a day.

Patient 8, a woman, aged 46, had an original blood sugar of 333 mg. per cent and urine sugar 8.5 per cent. Glycosuria had been first discovered ten months previously; she had polyuria and polydipsia, had lost weight, and had chronic osteomyelitis of the phalanx of the thumb. The urine was sugar-free on 20 Gm. of carbohydrate, 50 Gm. of protein and 190 Gm. of fat. Insulin had been started seven months previously, the dose being 12 units twice a day.

Patient 7, a man, aged 50, had an original blood sugar of 250 mg. per cent and urine sugar 1.43 per cent. Glycosuria had been first dis-

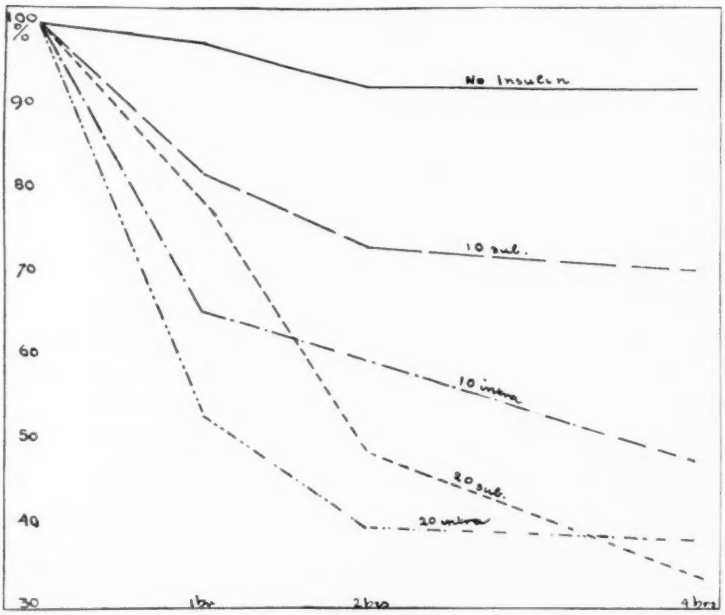

Chart 5.—Effect on blood sugar level in a case of mild diabetes of subcutaneous and intradermal insulin injections.

covered six years and eleven months previously; he had polyuria, polydipsia and polyphagia; he had lost weight and had a slight blurring of vision. The urine was sugar-free on 30 Gm. of carbohydrate, 50 Gm. of protein and 250 Gm. of fat. Insulin had been started fourteen months previously, the dose being 10 units twice a day. The patient was of the neurotic, emotional type.

Patient 9, a man, aged 55, had an original blood sugar of 666 mg. per cent and urine sugar 4 per cent (155 Gm.). Glycosuria had been first discovered one and a half years previously; he had polyuria, polydipsia and polyphagia; he had lost weight and suffered from weakness.

He was put on insulin treatment at the time the tests were started; 20 units twice a day was increased to 30 units twice a day and then after one month progressively decreased until he was receiving none five months after the beginning of the treatment. He was on a diet of 80 Gm. of carbohydrate, 80 Gm. of protein and 140 Gm. of fat. Five and one-half months after the beginning of the insulin treatment the urine was sugar-free on a diet of 120 Gm. of carbohydrate, 80 Gm. of protein and 150 Gm. of fat and no insulin. He gained 13 pounds (5.9 Kg.) in weight and is working. The fasting blood sugar is 160 mg. per cent. The gradual decrease in this patient's fasting blood sugar level under insulin treatment and his increase in tolerance is striking (Table 1).

The tests in this group show a still more prolonged blood sugar lowering effect of the insulin by both methods of administration. The difference in the effect on the blood sugar level between the two methods is on the average most marked at the second and fourth hour. The greatest difference in the blood sugar lowering effect between the two methods of administration occurs at a later period after injection than

TABLE 1.—*Results of Insulin Treatment in Case 9*

	Dates						
	Nov. 18	Nov. 28	Dec. 5	Dec. 12	Dec. 19	Jan. 14	Jan. 28
Fasting blood sugar in mg. per cent...	666	500	450	360	204	180	160
Urine sugar at time of blood sugar, per cent.....	1.8	2.6	2.5	2.2	0	0	0

in the previously described group. On the other hand, there is a greater variation in the degrees of difference in the effect of the two methods at the first hour when the individual curves in this group of cases are compared. The curve for Case 11 (Chart 6) has been chosen as the most typical for this group. Twenty minute tests carried out in three of these cases showed conclusively that the intradermal injection results in an earlier onset as well as in a greater hypoglycemic effect.

D. *Severe Diabetes Mellitus (Insulin Treatment).*—There were three cases in this group:

Patient 13, a woman, aged 16, had an original blood sugar of 364 mg. per cent and urine sugar 2 per cent. Glycosuria had been first discovered twenty months previously; the patient was sugar-free only on starvation. Insulin treatment was started nineteen months previously. The dose previous to the tests was 15 units twice a day. The symptoms were amenorrhea (menses had begun at 13½ years and were regular up to one month before sugar was discovered) and marked depression of tolerance secondary to any slight infection and to nervous and emotional strains.

Patient 15, a woman, aged 26, had an original blood sugar of 364 mg. per cent and urine sugar 1.6 per cent. Glycosuria had been first discovered four years and eight months previously following a toxemia of pregnancy; she had polyuria and polydipsia, had lost weight and was sugar-free on starvation only. Insulin treatment had been started eighteen months before examination, the dose being 10 units twice a day. This was gradually increased to 30 units twice a day. She went through a second pregnancy, stillbirth resulting. The insulin dose was now 20 units three times daily. The patient was of an emotional, neurotic

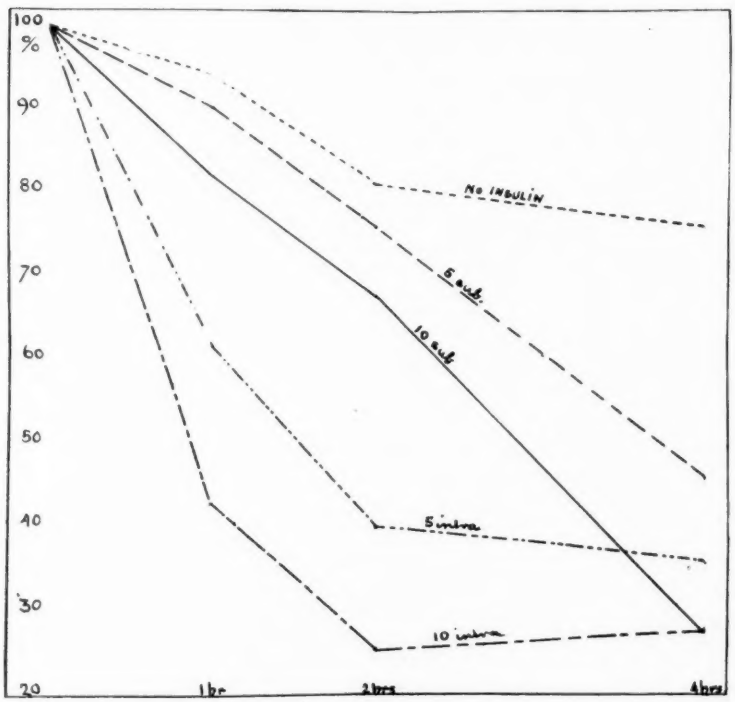

Chart 6.—Effect on blood sugar level in a case of moderately severe diabetes of subcutaneous and intradermal insulin injections.

type. The depression of the tolerance was marked following slight infections and emotional strains.

Patient 14, a woman, aged 41, had an original blood sugar of 243 mg. per cent and urine sugar 2.9 per cent. Glycosuria had been first discovered three years and ten months previously; she had moderate polyuria, polydipsia, polyphagia and pruritus; she had lost weight and was sugar-free on starvation only. Insulin treatment had been started

eighteen months before examination, 20 units three times daily. The patient was of phlegmatic type.

The reaction to the insulin injections in this group differs from the curves previously discussed in that the first hour effect of the intradermal dose is slight if not actually reversed, i. e., an increase in blood sugar level. During the second hour the drop is slight, and becomes pronounced only in the last period. The subcutaneous injection results in a slightly greater drop in the blood sugar level at the first hour, a more pronounced effect at the second hour and the level reached at the fourth hour is still below that reached following an intradermal injection of like

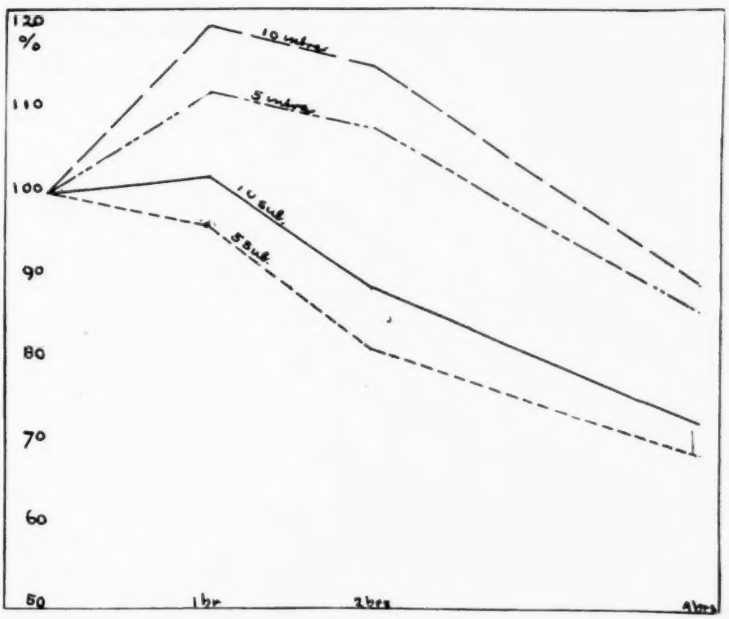

Chart 7.—Effect on blood sugar level in a case of severe diabetes of subcutaneous and intradermal insulin injections.

dosage. The curves obtained in the tests on Patient 14 are shown in Chart 7. The subcutaneous injections of from 5 and 10 units had practically no effect on the blood sugar level at the first hour, but a decided effect at the second and the fourth hour. The intradermal injections of like doses were followed by a decided rise in the blood sugar level at the first hour, a negligible drop from that level at the second hour, and a decided drop, reaching 12 and 14 per cent below the initial blood sugar level, at the fourth hour. The depression in the blood sugar level obtained by the subcutaneous doses was not reached,

TABLE 2.—*Blood Sugar Following Intradermal and Subcutaneous Insulin Injections in Diabetes Mellitus*

Case	Insulin Units	Insulin How Given	Blood Sugar Before Insulin, Mg. per Cent	Blood Sugar Following Injection in Percentage of Initial Value 1 Hour	2 Hours	4 Hours	Sugar Excretion in Urine, Gm. Before	After Insulin	Food Minutes After	Food Total Available Carbohydrate
1	5	Intradermally	156	55	63	65	0	0	85	3.2
	5	Subcutaneously	123	72	69	76	0	0	113	3.2
	10	Intradermally	168	48	53	61	0	0	120	13.2
	10	Subcutaneously	208	56	35	50	0	0	85	27.6
2	5	Intradermally	114	74	79	97	Trace	0	Fasting	
	5	Subcutaneously	129	89	84	84	Trace	0	Fasting	
3	5	Intradermally	118	64	72	79	Trace	0	105	29.0
	5	Subcutaneously	111	77	71	84	Trace	0	110	29.0
	10	Intradermally	108	51	67	78	Trace	0	120	29.0
	10	Subcutaneously	114	65	69	75	Trace	0	110	29.0
4	10	Intradermally	175	91	73	63	Trace	0	Fasting	
	10	Subcutaneously	196	93	80	76	Trace	0	Fasting	
5	10	Intradermally	222	66	60	48	0.23	0.36	80	45.0
	10	Subcutaneously	282	81	74	71	No specimen obtained		115	50.0
	20	Intradermally	298	53	40	38	0.95	1.37	130	40.7
	20	Subcutaneously	250	80	50	35	0.23	0.67	Fasting	
	No insulin		256	98	93	93	0.46	1.11	145	45.0
6	10	Intradermally	260	50	34	39	0.56	0	Fasting	
	10	Subcutaneously	210	90	58	43	0	0	Fasting	
7	5	Intradermally	408	82	73	58	1.98	4.89	108	31.7
	5	Subcutaneously	385	84	68	65	3.60	7.68	70	31.7
	10	Intradermally	371	63	48	49	1.53	0.52	90	38.4
	10	Subcutaneously	400	87	71	40	3.15	2.67	80	45.6
	No insulin		348	96	94	94	1.82	4.33	115	40.0
8	5	Intradermally	340	91	80	67	1.50	4.40	120	17.8
	5	Subcutaneously	270	106	86	74	0.96	3.39	120	8.3
	10	Intradermally	352	86	74	54	2.08	4.76	120	17.8
	10	Subcutaneously	377	96	83	69	2.58	5.58	120	23.6
	No insulin		346	93	93	74	2.28	5.37	120	10.1
9	5	Intradermally	666	88	86	62	3.37	5.52	170	14.4
	5	Subcutaneously	500	100	93	67	2.11	11.65	Fasting	
	10	Intradermally	450	78	69	57	4.90	7.55	Fasting	
	10	Subcutaneously	360	84	65	46	3.74	4.41	Fasting	
	10	Intradermally	204	75	65	52	0	0	Fasting	
	5	Intradermally	180	74	66	53	0	0	Fasting	
	5	Intradermally	200	77	69	60	0	0	Fasting (epinephrin)	
	5	Subcutaneously	160	81	68	54	0	0	Fasting (epinephrin)	
10	5	Intradermally	377	88	75	56	0.95	1.60	80	38.4
	5	Subcutaneously	286	85	80	64	0.33	1.04	60	28.4
	10	Intradermally	235	68	34	29	0.04	0.11	60	21.9
	10	Subcutaneously	274	72	74	49	0.08	0.35	95	21.9
11	5	Intradermally	317	60	40	36	3.90	1.15	110	25.7
	5	Subcutaneously	256	90	76	46	0.17	0.12	Fasting	
	10	Intradermally	308	43	26	28	3.50	0.34	120	31.3
	10	Subcutaneously	268	82	68	28	4.30	1.75	120	31.3
	No insulin		364	94	81	76	7.16	3.47	150	47.9
12	5	Intradermally	190	88	68	43	0	0	67	20.9
	5	Subcutaneously	177	97	87	68	0	0	75	23.6
	10	Intradermally	250	84	74	40	0.81	0.88	Not fasting	
	10	Subcutaneously	250	118	76	67	No specimen obtained		Not fasting	
	20	Intradermally	307	93	65	41	1.00	1.51	Not fasting	
	20	Subcutaneously	286	96	84	67	1.31	1.65	Not fasting	
	No insulin		400	95	91	96	2.45	10.50	60	41.4
13	5	Intradermally	364	86	82	67	3.22	2.22	Fasting	
	5	Subcutaneously	400	90	78	68	5.08	6.04	Fasting	
14	5	Intradermally	385	112	108	86	2.10	13.64	75	21.0
	5	Subcutaneously	434	96	81	69	2.87	12.00	105	25.8
	10	Intradermally	346	120	115	85	0.29	0.34	Fasting	
	10	Subcutaneously	345	102	88	73	1.13	2.59	Fasting	
15	10	Intradermally	244	87	100	90	Trace	0.28	Fasting	
	10	Subcutaneously	358	100	79	62	5.32	1.36	120	20.0

however. One set of these curves was run with the patient in a fasting condition while the other set was run following a meal of 22 Gm. of total available carbohydrate, taken ninety minutes before. The increase following the intradermal injection cannot be attributed solely to resorption from the gastro-intestinal tract for the rise in blood sugar occurred also in the fasting condition.

VI

The original blood sugar figures from which these curves were obtained, as well as the figures of the other cases, will be found in Table 2. The blood sugar determinations preceding the insulin injections are given in absolute numbers, i. e., milligrams per cent. The determinations at later time intervals are given in percentage of this initial value for the purpose of comparison.

TABLE 3.—*Blood Sugar Levels Following Intradermal and Subcutaneous Injections of Five Units of Insulin U-40*

	Blood Sugar Following Intradermal Injection				Blood Sugar Following Subcutaneous Injection				
	Mg. per Cent	Percentage of Initial Value			Mg. per Cent	Percentage of Initial Value			
Case	Before Injection	20 Minutes After	40 Minutes After	60 Minutes After	Before Injection	20 Minutes After	40 Minutes After	60 Minutes After	Food
11	210	95	86	76	...	..	..	..	Fasting
12	215	97	90	88	237	101	101	94	Fasting
16	185	97	93	84	244	99	95	94	Fasting
7	304	95	93	90	318	105	100	90	Black coffee
9	158	96	79	58	177	95	88	83	Fasting
5	182	98	84	78	192	96	91	87	Fasting
Average.....		95.5	87.5	79.0		99.2	95.0	89.6	
Average drop in percentage.....		4.5	12.5	21.0		0.8	5.0	10.4	
Per unit.....		0.9	2.5	4.2		0.16	1.0	2.1	

In a number of cases the blood sugar level was determined at the same intervals but without the insulin injection. In six additional series of one hour only, the blood sugars were determined at twenty minute intervals following the injections and these determinations are given in Table 3.

From the twenty minute series (Chart 2) it is apparent that there is a blood sugar lowering effect of intradermally injected insulin before an effective amount of the hormone can possibly be present in the blood stream for the subcutaneously administered equal dose of insulin shows no such effect twenty minutes after the injection. From the observations reported in the foregoing it is concluded that insulin injected intradermally must have an initial specific action produced in some way other than through the usual contact of the hormone with the tissue fluids and cells.

Summarizing the four hour experiments given in Table 2, it is shown that: twenty-nine, that is, 86 per cent of the thirty-three four

hour series, show a greater reduction in the blood sugar level at the first hour following the intradermal injection than at the first hour following the subcutaneous injection of an equal dose. At the second hour, twenty-three (70 per cent) of the intradermal injections resulted in a lower blood sugar level than did the subcutaneous injections. At

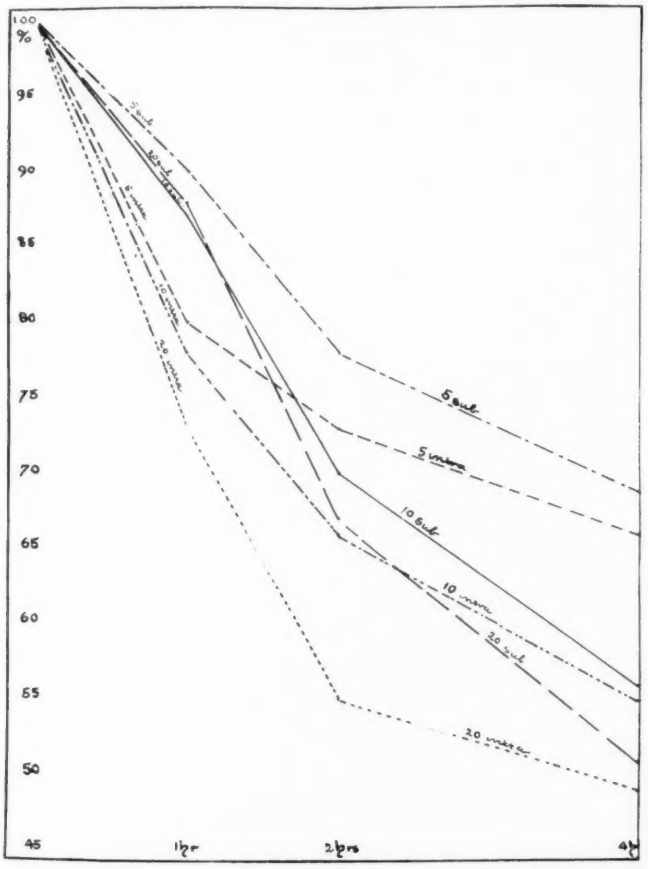

Chart 8.—Composite curves of thirty-three series showing effect on blood sugar level of subcutaneous and intradermal insulin injections (Table 2).

the fourth hour, twenty (67 per cent) of the series showed a greater hypoglycemia with intradermal administration.

The difference in the response to the two methods of administration as manifested by the hypoglycemic effect is most striking with the smallest doses (i. e., 5 units) and at the first hour after the injection.

Chart 8 gives the composite curves of all the 5 and 10 unit series. The fact that the maximum difference falls at the first hour and the gradual decrease in this difference at the subsequent time intervals is shown in this curve.

When we compare typical curves of the various groups, the greater hypoglycemic effect of the insulin injected intradermally as compared to the effect of a like dose given subcutaneously may be noted in all groups except in the severe cases. This difference in effect occurs at the first hour following the injection, and decreases in the mild cases after the first hour. The difference in effect is progressively extended to the later intervals of the experiments with the increase in severity of the disease. In the severe cases the difference at the first hour is absent or reversed, and the subcutaneous injection results in a greater blood sugar lowering effect which persists throughout the period of the experiment.

In the normal there is little difference if any between the hypoglycemic effect of insulin administered intradermally and that of a like dose given subcutaneously. Probably the defense mechanism of the body to the insulin, especially glycogenolysis, is initiated at an early stage and cuts down the greater hypoglycemic effect of the intradermally administered dose. This mechanism also causes the recovery toward the original blood sugar level to be well under way at the second hour following the injection. In mild diabetes this mechanism manifests itself at the second hour following an intradermal injection though to a smaller degree, while for the subcutaneously administered dose the hypoglycemic effect of insulin extends into the second hour and recovery toward the original level begins in the last period. The onset of glycogenolysis is not determined solely by the extent of the hypoglycemic effect; the intensity of the stimulus due to the insulin injection also is a factor. In the majority of cases the recovery toward the original level starts from a slightly lower blood sugar level following subcutaneous injection than following an intradermal injection. The nearer to normal the condition of cell metabolism, the more quickly will the cells receive and react to glycolytic stimuli due to the presence of the hormone, or to glycogenolytic stimuli due to the abnormally low blood sugar level. In the severe diabetic case glycolytic activity as well as glycogenetic activity is greatly impaired or absent. The first effect of the intradermal injection may result in an increase in the blood sugar due to glucogenic activity of the cells.

The reaction of the individual to either subcutaneous or intradermal insulin administration would seem to depend in its degree on (1) the condition of carbohydrate metabolism at the time; (2) the reactivity of the nervous system to chemical stimuli; (3) the amount of glycogen storage in the liver and in the muscles, and (4) the rate of resorption of injected insulin into the circulation.

Insulin injected subcutaneously enters the blood stream and is brought to the tissues more promptly than when the same dose is given between the layers of the skin. Kasahara [5] showed that the resorption of true solutions, colloidal solutions and cell and bacterial suspensions when introduced intradermally is materially delayed as compared to identical injections administered subcutaneously. If the increased response to an intradermal injection at the first hour following the injection were due to a quicker resorption and entrance in greater quantity of the hormone into the blood stream, increasing the dose should result in an even greater difference in the lowering of the blood sugar between the two modes of injection. However, the reverse is the fact. The results cannot therefore be explained by a quicker and more complete resorption of the intradermally introduced insulin.

The blood sugar decrease must always be preceded by a biologic insulin action. If the decrease is observed within twenty minutes after the injection the insulin action must have taken place before the end of this period. There is no possibility of establishing a relationship between a postponed resorption and a more rapid effect, if the activity of the insulin is dependent on the presence of the hormone in the circulation. In 86 per cent of the experiments the intradermal injection was followed by greater lowering of the blood sugar level at the first hour following the injection than the subcutaneous injection of like dosage under standard conditions. This also cannot be explained by the delayed absorption if the activity of the insulin were dependent on the presence of the hormone in the circulation. It is also to be considered that the pathway of absorption from the intradermal layers of the skin to the circulation is over a longer route and it may be postulated that in that case the loss by adsorption is greater and hence the amount of active material which reaches the circulation is less than when insulin is administered subcutaneously. This loss by adsorption will be the greater the larger the dose. The excretion in the urine and loss of active insulin in the circulation must be the same, no matter from what region the insulin has entered the circulatory system.

The absorption from the subcutaneous area is more rapid and larger quantities of insulin are present in the circulation and in the tissues at a given time following the subcutaneous injection, and hence, a small dose will be exhausted more rapidly. This is demonstrated by the relatively prolonged effect of small doses introduced intradermally. When a small dose, i. e., 5 units, is used the effect of the intradermal dose will outlast that of the subcutaneous. With larger doses the loss by adsorption is relatively greater and the effect is comparatively prolonged. Increasing the doses of insulin injected intradermally does not

5. Kasahara: Ztschr. f. d. ges. exper. Med. **44**:294, 1925.

result in a corresponding increase in effect, that is, a smaller dose has a greater per unit effect, as shown by the blood sugar determination, than the larger dose at the first hour following the injection. It may be concluded that the direct hormone action of insulin in the blood and tissues is not the only factor involved in its physiologic action. The evidence of the existence of another factor is supplied by the reaction to intradermal injection and, as has been shown, this factor must even be effective in the absence of the circulating hormone.

VII

If the hormone activity of the insulin consists of an effect on the sugar molecule, either by causing a molecular rearrangement to a more reactive form or by favoring the formation of a more reactive compound, such an activity should be observable in the blood in vitro by an increased glycolysis.

If the insulin in addition causes increased glycogenetic activity or storage within the cells in some other nonreducing form and thereby removes the glucose from the blood and the tissues, the glycolytic activity of the blood will not express this activity of the insulin.

Glycolytic activity tests were made for the purpose of determining if the glycolytic activity of the blood increases after insulin administration or not. A marked increase of the glycolytic activity after the administration of insulin may be attributed to the entrance of the hormone into the blood stream or tissues.

The glycolytic activity as it occurs in the blood, determined in vitro, indicates the glycolysis taking place in vivo. It may be taken as a certain measure of physiologic glycolysis only if the limitations inherent in the method are recognized.

In the living body conditions favor the reaction. Oxygen is constantly supplied, the p_H is maintained, the reaction products are removed, and the substrate is constantly replenished. None of these conditions is fulfilled in vitro. Furthermore, the effect of the anticoagulant must also be taken into account. The measurement of glycolytic activity of the blood must be carried out under standard conditions in order to minimize the experimental error. The temperature is a factor and the erythrocytes must be morphologically intact in order that glycolytic activity may proceed. The glycolytic activity determined at half-hour intervals was found to proceed in almost linear progression up to two and a half hours. A two hour incubation period was therefore chosen as one most likely to give distinct difference in the blood sugar. The anticoagulant was used in constant proportion. The blood was drawn and divided into aliquot parts, one of which was immediately precipitated while the other, carefully stoppered, was kept in the incubator at

body temperature for two hours. At the end of the incubation period the water dilution was added and the proteins precipitated. The time allowed for the precipitation of the proteins and for the filtration, as well as the size and the thickness of the filter paper, were carefully standardized. Table 4 gives the results of the individual experiments. In Chart 9 the average blood sugar levels following intradermal and subcutaneous insulin injections as well as the glycolytic activities of these bloods are shown. The blood sugar level as well as the glycolytic activity are expressed in percentage of the initial value, i. e., the value preceding the injection.

TABLE 4.—*Glycolysis Following Intradermal and Subcutaneous Insulin Injections*

Case	Initial Blood Sugar Concentration, Mg. per Cent	Insulin: Unit	Insulin: How Given	Two Hours Glycolysis in Mg. per Cent of Absolute Value of Blood Sugar; Time After Injection: Before	1 Hf.	2 Hrs.	4 Hrs.	Two Hours Glycolysis in Percentage of Initial Glycolysis; Time After Injection: 1 Hr.	2 Hrs.	4 Hrs.	Time After Injection of Lowest Blood Sugar, Hrs.	Food, If Any: Minutes After	Total Available Carbohydrate
13	364	5	Intradermally	13	13	25	34	100	192	261	4	Fasting	
	400	5	Subcutaneously	10	29	23	24	290	230	240	4	Fasting	
1	156	5	Intradermally	17	14	20	7	82	118	41	1	83	3.2
	123	5	Subcutaneously	20	15	18	14	75	90	70	2	113	3.2
	168	10	Intradermally	17	25	34	17	147	200	100	1	120	13.2
	208	10	Subcutaneously	8	12	33	13	150	412	162	2	85	27.6
7	371	10	Intradermally	19	14	9	5	74	47	26	2	90	38.6
	400	10	Subcutaneously	22	16	32	22	73	145	100	4	80	45.6
9	450	10	Intradermally	23	15	17	22	65	74	99	4	Fasting	
	360	10	Subcutaneously	17	29	13	22	170	77	129	4	Fasting	
	204	10	Intradermally	17	16	18	22	94	106	129	4	Fasting	
17	140	10	Intradermally	45	29	52	25	64	116	56	1	60	48.8
	98	10	Subcutaneously	22	27	21	17	123	96	78	4	155	35.5
	109	5	Intradermally	19	12	8	8	63	42	42	1	155	53.7
	105	5	Subcutaneously	23	30	27	9	131	118	39	1	130	53.7
11	317	5	Intradermally	23	23	33	13	100	144	57	4	110	25.7
	256	5	Subcutaneously	15	13	16	6	67	107	40	4	Fasting	
6	208	10	Intradermally	31	24	22	16	78	71	52	4	Fasting	
	220	10	Subcutaneously	24	27	22	12	113	92	50	4	Fasting	
3	118	5	Intradermally	18	7	12	7	39	67	39	1	105	29.0
	111	5	Subcutaneously	17	18	20	17	106	118	100	2	110	29.0
	108	10	Intradermally	23	20	22	24	87	96	105	1	120	29.0
	113	10	Subcutaneously	26	23	19	33	88	73	127	1	110	29.0
Average		5	Intradermally					77	113	88			
		5	Subcutaneously					134	133	98			
		10	Intradermally					87	101	84			
		10	Subcutaneously					120	151	108			

It may be seen that the glycolytic activity does not run parallel to the blood sugar lowering effect. While the average blood sugar lowering effect of the intradermal injection at the first and second hour after the injection exceeds that of the subcutaneously administered insulin, the average glycolysis following intradermal injections is less at the first hour following the injection than before the administration of the insulin, and at the second hour is found only slightly increased above the first, initial value. The glycolysis following subcutaneous injection is increased at the first hour and still more so at the second hour following the injection.

This observation may indicate that the increase of the glycolytic activity is due to an increased concentration of the hormone in the circulation. The average decrease of the glycolytic activity after intradermal injection of insulin as compared to the glycolytic effect of a subcutaneous injection proves at least that there is no such increase, and points rather to a delayed adsorption of the insulin into the circulation.

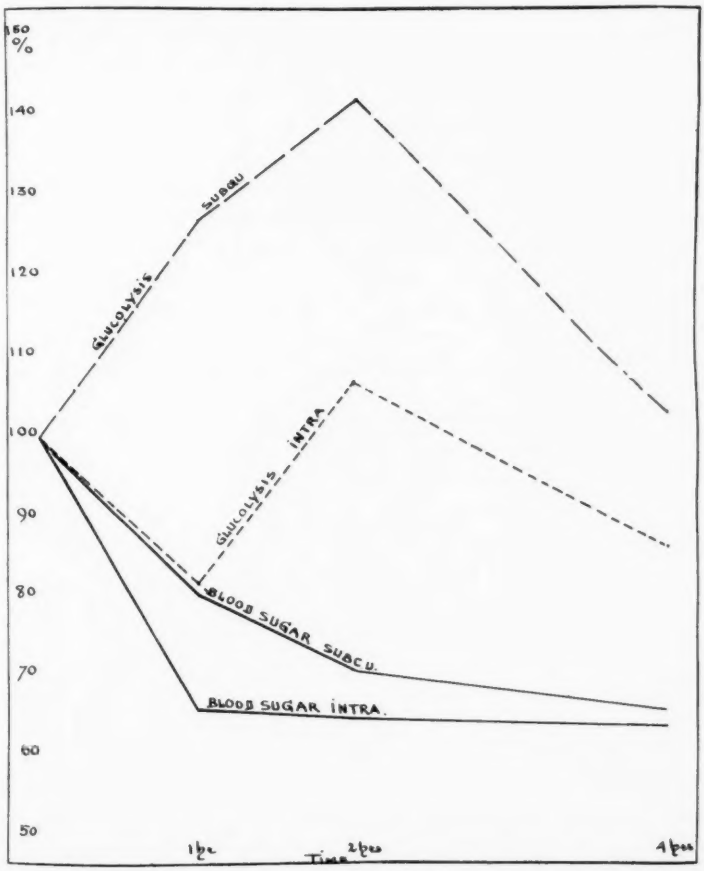

Chart 9.—Composite curves of nine series showing effect of subcutaneous and intradermal insulin injections on the glycolytic activity of the blood (Table 4).

The observed average decrease of the glycolytic activity after the intradermal injection may be due to a defensive action or it may be due to a slightly lowered cell volume often observed to follow insulin injections. In view of the many factors that influence this activity a great many more experiments should be done before final conclu-

sions are drawn. The influence of dietary factors as well as the effect of hypoglycemia on glycolysis must be studied before any definite conclusions as to a relationship between the pancreatic hormone and the glycolytic activity of the blood in vitro can be reached. For instance, we have found the glycolytic activity of blood to increase from 30 to 50 per cent one hour after the intake of food as compared to the fasting condition. It has also been noticed that pronounced depression of the blood sugar level is followed by a material reduction in the glycolytic activity, probably due in part to the small concentration of the substrate. The negative results reported in the literature in the matter of increase in glycolysis following insulin injection may perhaps be explained from the foregoing. If the extent of glycolysis is determined at the height of insulin activity (e. g., during insulin shock) it will not be found increased but may be even depressed below the value found with a normal supply of substrate.

VIII

There would appear to be two possible ways by which insulin when in the circulation may exert its physiologic activity: 1. Fragmentation of the blood sugar molecule. 2. Contact with the liver, the muscles and perhaps other organs, which are stimulated to exert their normal activity in carbohydrate metabolism. When insulin is given intradermally, in which case, as has been shown in the twenty minute series, it has a decided effect on the blood sugar level before there can have been absorption of sufficient amount into the circulation, these two methods of action could not be held accountable for the observed effect.

The absorption of the effective hormone into the circulation is retarded when the insulin is administered intradermally. The demonstrated delayed absorption from the intradermal layers of the skin,[5] as well as the results of the determinations of glycolysis of bloods taken after insulin injections, justify the assumption that the initial (twenty minutes) effect of the insulin given intradermally is due to an activity exerted before it has entered the circulation.

In the absence of insulin administration there are three known ways by which the blood sugar level may be decreased: (1) muscle activity, resulting in increased oxidation; (2) specific hyperfunction of the pancreas causing increased glucose catabolism, and (3) glycogen formation in the liver and in the muscles.

Muscle activity as a reason for the decrease in blood sugar observed in our tests can be eliminated. Tests on animals have shown that insulin, no matter how injected, is not effective if there has been muscular activity. Such an activity results in hyperglycemia which hides

for more than an hour any blood sugar lowering effect of the injected insulin.[6]

The decrease of the blood sugar level at the first hour following intradermal insulin injection observed in diabetic cases can be explained by increased pancreatic activity only if large quantities of the pancreatic hormone were thereby caused to be introduced into the circulation. This again should lead to an increase in the glycolysis of the blood which did not manifest itself.

The third possibility mentioned is the lowering of the blood sugar level through increased glycogen formation in the liver and tissues. The first effect of an intradermal insulin injection may be such an increase in the glycogenetic function of the liver cells stimulated by a nerve pathway.

It is known that glycogen is formed rapidly. A 30 per cent loss in the blood sugar in one hour may be accounted for by glycogen formation. Such a decrease in an individual with a normal blood volume would mean that approximately 1.65 Gm. of glucose had been polymerized into glycogen in this period.

Claude Bernard demonstrated that the liver receives autonomic impulses from the sugar center in the medulla which travel along the splanchnic nerve and cause the formation of glucose from glycogen with a resulting hyperglycemia. It is also known that parasympathetic stimuli lead to the formation of glycogen in the liver.[7] If activation of the glycogenetic function of the liver cells occurs by way of a nerve action secondary to the injection of insulin into the skin, the chief or sole pathway of the stimulus must be by way of the parasympathetic fibers of the autonomic nervous system.

Eiger,[7] working with turtles, showed that stimulation of the peripheral end of the cut vagus caused increased glycogenesis, despite exclusion of the pancreatic activity. Meyer[8] showed that injection of pancreatic extract inhibits glycogenolysis in the liver. From these experiments it is to be assumed that stimuli may travel by way of the parasympathetic nerves to the liver and there cause actual increased liver cell metabolism, and also that such stimuli may travel to the pancreas; in this way an equivalent internal secretory influence of the liver cell metabolism may be registered. In both cases parasympathetic stimulation results in the inhibition of glycogenolysis.[9] Minkowski's experiments have shown that not only extirpation of the pancreas but

6. Corbitt, H. B.: Am. J. Pharm. A. **14**:108, 1925.
7. Eiger, M.: Centralbl. f. Physiol. **30**:445, 1915.
8. Meyer, H., in Mayer-Gottleib: Experimentelle Pharmakologie, Berlin, 1922.
9. Quoted from Müller, L. R.: Die Lebensnerven, Berlin, Julius Springer, 1922.

also disconnection of the nerves between the pancreas, the liver and the duodenum results in diabetic symptoms.[10]

A brief period of hypoglycemia must follow glycogenesis. Clinical and experimental studies bear out the assumption that glycogenesis is responsible for an initial drop in the blood sugar level following intradermal insulin injection.

The glycogenetic function of the liver in health and in cases of mild diabetes is decreased if the liver is rich in glycogen, and the intradermal insulin effect has been found to be decreased in such cases after food intake. In severe diabetes the glycogenetic function of the liver is absent or much reduced and in such cases only a small difference, if any, between the two modes of administration could be demonstrated at the first hour period.

The difference in effect between the intradermal and the subcutaneous insulin injections in nondiabetic cases is small and variable, i. e., the subcutaneous injection may be more effective than the intradermal. This observation may also be explained on the basis of glycogen storage.

The smaller effect of the intradermal injections in severe diabetes as well as the absence of difference in effect between the two methods of administration in well nourished nondiabetic subjects can be explained by limitation of the glycogen forming potential of the liver cells.

Glycogen formation is limited in healthy subjects after eating because at that time glycogen is accumulated in the liver. In severe diabetes the function of glycogen formation is pathologically decreased. However, in either case decreased glycogenesis can only limit the blood sugar lowering process if this process consists, at least in part, in removal of the sugar from the circulation through glycogen formation. If it consists exclusively of fragmentation or oxidation of the glucose present in the blood and in the tissue fluids, the amount of glycogen present in the liver or the impairment of the glycogenetic function of the liver cells can have no influence.

Estimation of the respiratory quotient may be another method applicable to the determination of the question as to whether or not glycogenesis follows intradermal insulin injection. Glycogen formation from glucose does not increase the respiratory quotient whereas oxidation of glucose increases it. A difference in the insulin effect on the respiratory quotient shortly after the injection and at later intervals might be determinable by very exact experimental work. However, the brief period during which glycogen formation alone is responsible for the blood

10. Minkowski: Arch. f. exper. Path. u. Pharmakol. **30**:371, 1893; ibid. **53**: 331, 1905; Berl. klin. Wchnschr., 1890, No. 8.

sugar lowering effect is so close to the injection itself that it would be difficult to obtain accurate results. Slight excitement of the patient, which is unavoidable after an injection, and the fact that within about thirty minutes the hormone action becomes effective would prevent a correct interpretation. Furthermore, the difference from the basal rate caused by the oxidation of about 1.5 Gm. of sugar is too small to be measured by the clinical calorimetric methods at present at our disposal.

IX

The foregoing discussion leads to the assumption that a nerve stimulus resulting from an intradermal injection of insulin causes glycogenesis. Experimental evidence of the physiologic effectiveness of such a stimulus was obtained by blocking the particular nerve fibers.

The experiments were carried out with rabbits. The animals were injected with 10 mg. of atropin per kilogram of body weight simultaneously with either intradermal, subcutaneous or intravenous insulin injections. The blood sugar of these animals as well as of control animals that did not receive the atropin injection, was determined half an hour after the injections. The effect of the intradermal injection on the blood sugar was much less in the atropinized rabbits than in the nonatropinized controls, the average showing 50 per cent difference. The average effect of the subcutaneous as well as the average effect of the intravenous injections of insulin was found to be the same in the atropinized as in the nonatropinized rabbits. The reason for this can only be that the nerve action of intradermally injected insulin is decreased or eliminated by atropin. In atropinized animals the hormone effect which follows absorption of the insulin into the circulation is the only mechanism of physiologic action, irrespective of the method of administration.

The results of these experiments are given in Chart 10.

The reduction in the hypoglycemic effect of an intradermal injection of insulin following the elimination of the nerve action by atropin is additional evidence that a nerve impulse is a prerequisite for the early insulin effect initiated by intradermal administration.

The use of epinephrin, which also blocks the parasympathetic nerves by increasing the tonus of the sympathetic, is of no value in such an experiment since one of its pharmacologic effects is increased glucose formation. The resulting hyperglycemia obscures the insulin effect. Pilocarpin in small doses increases the parasympathetic tonus, but is without influence on the insulin effect, and the usual difference between the intradermal and the subcutaneous insulin administration is observed when accompanied by injections of small doses of pilocarpin.

X

The quantitative determination of the urinary sugar excretion coincident with the blood sugar determinations following intradermal and subcutaneous insulin injections showed that the total amount of sugar excreted following an intradermal injection is decidedly less than that following a subcutaneous injection of a like dose under the same conditions. This lessened excretion cannot be solely attributed to the relatively greater and the quicker hypoglycemic effect of the intradermally injected insulin. The blood volume may be considered 8.8 per cent of the body weight. The total amount of blood sugar before insulin injection and at

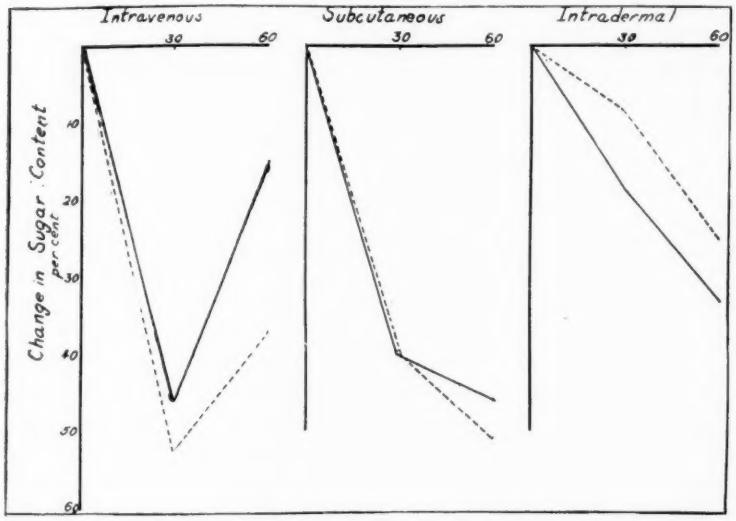

Chart 10.—Average curves of a series of seven normal rabbits showing effect of atropin on action of insulin; solid line: insulin injection alone; broken line: atropin and insulin injection.

stated intervals following the injection is obtainable from the blood sugar estimations. The difference in the amount of blood sugar lost and the amount of sugar excreted in the urine at a given interval following insulin injection represents the amount of sugar metabolized during this period less the indeterminable factor represented by the augmentation of the blood sugar by glycogenolysis or by resorption of sugar from the intestinal tract or body tissues. Adherence to standard conditions in these tests reduced this error to an almost constant quantity which, for the purpose of these experiments, may be ignored.

The average of the urinary sugar excretion and the coincident reduction in total in blood sugar in one and in four hours following intradermal and subcutaneous insulin injections are shown in Chart 11. While it must be remembered that the quantities determined can only be considered approximate, they demonstrate a distinct difference in the amount of sugar metabolized following the two methods of insulin injection. With a small dose, insufficient in its hormone supply, the difference between the two methods of injection is marked at the first hour and still definite at the fourth hour. With double the dose the difference is not quite as great at the first hour as with the smaller dose, but at the fourth hour, when presumably full absorption has taken place, the difference is materially decreased.

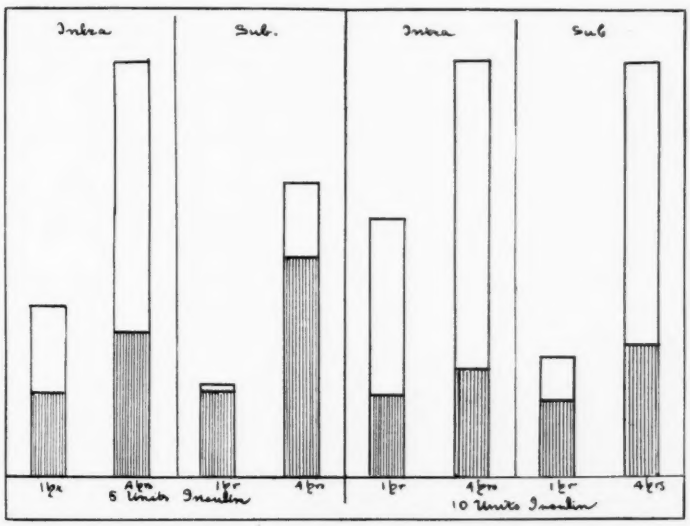

Chart 11.—Diminution in total blood sugar following intradermal and subcutaneous insulin injections: height of columns represents reduction in total blood sugar; shaded portions represent urinary sugar excretion; unshaded portions represent sugar metabolized.

The striking differences following the two methods of injection again point to two different mechanisms of physiologic action which are especially apparent at the first hour after the insulin injection.

CONCLUSION

The results of the experiments reported in this article lead to the conclusion that insulin injected intradermally acts immediately by way of an autonomic nerve pathway on the liver, intensifying its glycoge-

netic function. The effect of this stimulus is decreased or eliminated (*a*) if the glycogen storage in the liver is large; (*b*) if the glycogenetic function of the liver is pathologically decreased (severe diabetes), and (*c*) if substances are simultaneously injected which paralyze the parasympathetic fibers and thus disrupt this connection between the skin and the liver or if physiologically contrary stimuli overcome the parasympathetic impulses.

The nerve stimulus continues to act on the liver as long as active insulin is present in the intradermal depot. The glycogenetic activity of the liver at a given time does not depend on nerve impulses alone; the glycogen stores present in the liver as well as the severity of the diabetes are factors which must be considered when interpreting the differences obtained by the two methods of injection, in a given case.

A hormone action of the insulin in the body fluids does not take place in the first interval following an intradermal injection. The rate of absorption of insulin injected intradermally is slower than the rate of absorption of insulin injected subcutaneously and extends over a longer period. As insulin is gradually absorbed from the intradermal depot into the circulation, the direct or hormone action is added to the nerve action. Neither the point of onset of this hormone effect nor the period during which insulin is active exclusively by way of the nerve path are determinable from the blood sugar curves.

In nondiabetic patients and in patients with mild diabetes glucose formation by glycogenolysis due to the depression of the blood sugar level caused by the injected insulin has to be considered when drawing conclusions from the results obtained at the first hour following the injection. The hormone action of insulin in the circulation and in the tissue fluids is dependent only on the concentration, and the glucose formation by glycogenolysis secondary to depression of the glucose level below the normal must be taken into account.

Stimulation of glycogenesis by a nerve pathway and the hormone effect on the glucose molecule are two distinct methods of insulin action. The nerve effect is most prominent following the intradermal injection. It may be present, but to a much less extent if insulin is injected subcutaneously. Following an intravenous injection the nerve effect is almost entirely lacking. This probably explains the relatively small therapeutic value of the intravenous route of administration. Since the nerve effect, which stimulates glycogenesis in the liver, continues to act as long as active insulin is present in the skin, it is prolonged when absorption is delayed. Gradual absorption will also result in a less intense but a more prolonged hormone action within the blood and tissue fluids. Subcutaneous injections are not only followed by a less intense nerve effect but in addition, because of more rapid absorption, the hormone

effect is of shorter duration. Owing to the more rapid absorption the hormone effect is initiated at an earlier moment and sooner exhausted, especially if the dose is small. The amount of hormone entering the circulation after an intradermal injection of insulin depends on the extent of the loss of active material by adsorption.

The difference in effect found to result from different methods of insulin administration recalls the results of experiments in which nonspecific agents were employed.[11] The injection of nonspecific, nontoxic albumin into the human body causes a reflex action on the involuntary nervous system. The closer the injection is made to the derma, the more pronounced is this reaction.

Insulin by way of the parasympathetic nervous system stimulates the glycogenetic function of the liver and possibly other cells possessing glycogenetic activity and thereby removes sugar from the blood stream. This nerve effect continues as long as active insulin is present in the depot. The possibility is suggested that such a glycogenetic impulse might originate from any body tissues containing active insulin and supplied with parasympathetic nerve connections.

It may be mentioned that a number of experiments have been reported which apparently show the relation of insulin to the involuntary nervous system, such as (*a*) action similar to choline on the mucous membrane of the intestines;[12] (*b*) disturbing actions on the electrocardiogram,[13] and (*c*) blocking of insulin action by pharmacodynamic substances.[14]

Experiments are now being conducted to compare the known physiologic interrelation between the pancreas, the liver and other organs with the findings of the experiments which form the subject of this article. It has been shown that stimulation of the pancreas by nerve irritation leads to a stimulation of the glycogenetic function of the liver by way of nerve fibers recognized as parasympathetic or vasodilating. It is further known that under physiologic conditions the concentration of the pancreatic hormone in the circulation does not approach the concentration resulting from the injection of insulin in even moderate doses.

A sudden decrease of the blood sugar level in the circulation such as may be obtained by insulin injection creates impulses that act on the sugar center, and from here, in turn, impulses travel to the liver,

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11. Müller, E. F.: München. med. Wchnschr. **69**:1506 (Oct. 27) 1922; ibid. **69**:1753, 1922; Involuntary Nervous System: An Important Factor in Body's Resistance, Arch. Int. Med. **35**:796 (June) 1925.
12. Dresel, K., and Zimmer, H.: Biochem. Ztschr. **139**:463, 1923.
13. Von Haynal: Klin. Wchnschr. **4**:403 (Feb. 26) 1925.
14. Magenta and Biosotti: Compt. rend Soc. de biol. **89**:1125, 1923.

increasing the formation of glucose by local overbalance of the tonus of the sympathetic nerves.[16]

Insulin absorbed into the circulation lowers the blood sugar by increasing the glucose metabolism. The introduction of the pancreatic hormone into the circulation in large concentration cannot be compared to the normal physiology of blood sugar level regulation which depends on the equilibrium between glycogenesis and glycogenolysis. The nerve effect following an intradermal injection of insulin resembles the physiologic activity of the pancreas, while the increased direct hormone effect obtained after absorption cannot be considered the counterpart of the physiologic process.

The neurol stimulation of glycogenetic activity cannot be separated from the hormone effect, but it is intensified by intradermal administration, while simultaneously the hormone effect, due to slower absorption and a certain increased loss by adsorption, is lessened. It remains to be seen whether better therapeutic results may be obtained by repeated intradermal administration of insulin, especially in the milder types of diabetes. It seems likely that a protracted intradermal treatment might be superior in therapeutic effect to the usual course of subcutaneous injections which do not stimulate the impaired function of the liver to the same extent. Such protracted glycogenetic impulses might lead to partial recovery or might at least check the progress of the disease. Severe cases in which there is great impairment or even absence of the glycogenetic function will remain the field for that method of insulin treatment which enhances glucose catabolism.

SUMMARY

A deposit of insulin in the body acts by a nerve stimulation which increases the glycogen forming function of the liver. This nerve stimulation is conducted parasympathetically. The effect is active as long as the insulin deposit exists as such. It is particularly strong if the insulin deposit is made in the skin because of its close relationship to the autonomic nervous system. The nerve effect is weaker after deposition of the insulin in organs in which absorption takes place rapidly, for instance, the subdermal tissues, and is lacking after intravenous administration. The hormone effect in the circulation and in the body tissues is relative to the dose but the neural effect of insulin does not depend on the dosage. Simultaneously with the beginning of the absorption from the insulin deposit and with the consequent entrance of insulin into the circulation the direct hormone effect is manifested. The nerve effect decreases simultaneously with the diminution of the insulin deposit outside of the circulation and disappears as the last part of the insulin deposit is absorbed.

16. Claude Bernard, quoted from Müller, L. R.: Die Lebensnerven, Berlin, Julius Springer, 1924.

GASTRIC AND DUODENAL ULCER

THEORETICAL AND CLINICAL STUDIES *

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Despite a tremendous amount of experimental, anatomic and clinical investigation, the problem of the pathogenesis of ulcer is not yet solved. A discussion of the various theories will not be attempted here. Only the general trend of thought will be indicated.

For many years ulcer was considered a local disease. It was thought that the original defect was produced by local causes such as vascular or traumatic lesions and that its chronic character was the result of the unrest and irritation inherent in the stomach. This theory still has many adherents, notably Aschoff.

A study of the recent literature, however, shows a tendency to consider ulcer a local consequence of a general bodily disturbance. For instance, von Bergmann [1] and his pupils, Westphal and Katsch,[2] following Eppinger and Hess, have found general "vagotonic" stigmas in ulcer patients. Friedman [3] has added a "sympathicotonic" group. Peritz and Fleischer [4] describe a "spasmophilia" of the whole person, while Kaufmann [5] speaks of a "visceral tetany."

A consideration of the evidence of these authors makes it seem probable that these neuropathic and spasmophilic phenomena do play an important rôle in the pathogenesis of ulcer. It seems more probable, however, that the truth includes both views and that ulcer as a disease entity results from local plus general causes. The purpose of this article is not to propose a new theory but to analyze the problem more fully in an attempt to reconcile the various theories. It includes an outline of one method of attacking the problem and also the observations made thus far.

Ulcer of the stomach or duodenum may be defined as a loss in the continuity of the mucous membrane. Conceivably such a defect or erosion may be produced readily by various causes, traumatic, chemical, mechanical, thermal, bacterial, arteriosclerotic, embolic, thrombotic, toxic and hemorrhagic. It seems probable that ulceration, at least superficial,

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1. Von Bergmann, G.: Berl. klin. Wchnschr. **22**:524, 1918.
2. Katsch, G., and Westphal, C.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **26**: 391, 1913.
3. Friedman, G. A.: Peptic Ulcer, J. A. M. A. **71**:1543 (Nov. 9) 1918.
4. Peritz, G., and Fleischer, F.: Arch. f. Verdauungskr. **32**:243, 1923.
5. Kaufmann, J.: Am. J. M. Sc. **165**:67 (July) 1923.

is brought about by one or the other of these agents in almost every human stomach. These ulcers, in most cases, apparently heal completely, promptly, and without visible scarring. In some persons, however, such a primary erosion fails to heal and assumes the pathologic characteristics of round ulcer of the stomach or duodenum. It may remain superficial or progress deeper, may almost heal and then break down, or it may heal and recur. Whatever its outcome, however, it is chronic and this is its chief characteristic. In the experimental animal one may cause or institute an erosion or ulcer, but it invariably heals. If a piece of mucous membrane is excised with its submucosa and muscularis, leaving only the serosa intact, such an experimental ulcer in the dog's stomach invariably heals perfectly within a few weeks. Briefly, the most important feature of ulcer is not the cause of the primary erosion but its failure to heal. The solution of the ulcer problem will probably be found in a study of the conditions that tend to retard or prevent the process of healing. It is one of the purposes of this article to emphasize this phase of the problem.

Many theories have been advanced to account for the chronicity. These include (1) irritation (ingesta, acid, peristalsis); (2) infection (bacteria, toxins, fungi); (3) devitalization (thrombosis, embolism, arteriosclerosis, hemorrhage, angiospasm, myospasm), with subsequent digestion by acid and pepsin or regurgitated trypsin; (4) absence of substances (antipeptic ferments, mucus) that normally protect the gastric mucosa from autodigestion; (5) congenital weakness of the tissues locally (intestinal or other cell rests, malformations, arrested development); (6) mechanical irritation (at the "magenstrasse" and the isthmus), and (7) disturbances of the vegetative nervous system (vasomotor instability, hyperperistalsis, hypersecretion, myospasm). These are the most important theories. As yet, however, an explanation of the cause of chronic ulcer which harmonizes with the clinical and pathologic facts does not seem to be at hand.

A rational approach to the problem would seem to be a study of the physiology of inflammation with reference to the factors that may retard healing processes. What conditions—local or general—exist in these patients which may interfere with the normal or physiologic repair phase of the inflammatory process? This question involves difficult and unsettled problems concerning the physiology of inflammation. There are, nevertheless, certain valuable observations that concern our problem.

Undoubtedly, constant irritation of an injured site delays or prevents healing. Also a decreased vascular supply acts similarly. Conversely, lack of irritation and a good circulation locally seem to hasten the process of repair. There seems to be considerable evidence, furthermore, that the repair phase, at least, is largely dependent on vasomotor and other visceral nerve influences.

The general tendency of the investigators of repair in peptic ulcer has been to study the factors that irritate the sensory or afferent nerves. It has been repeatedly suggested that the mechanical, chemical and thermal irritation of food, the presence of acid and pepsin, and the tonic and peristaltic changes in stomach and duodenum supply the numerous sensory impulses that prevent the healing of the ulcer. This explanation, however, does not seem sufficient when we recall that these factors may be constantly present and yet a large number of more or less superficial ulcers or erosions presumably occur in the human stomach and apparently heal promptly and perfectly. Also the constant healing of such ulcers experimentally produced in animals would tend to substantiate this theoretical observation.

It seems more probable that a consideration of the motor responses to these sensory stimuli may lead us further in the problem. There is evidence, clinically, that there may exist locally a disturbance in the motor response in the direction of excess. For, in most cases, hyperperistalsis, hypersecretion, hypertonus, localized myospasm, and pylorospasm are present at some time or throughout the disease. Furthermore, arteriolar and capillary constriction, and spasm of the muscularis mucosa probably exist without being evident clinically. A consideration of the physiology of inflammation makes it probable that this local state of excessive motor response or overirritability interferes with healing. Theoretically this local overirritability might result from local or general causes: (1) repeated and excessive sensory stimuli; (2) overirritability of the responding tissues; (3) increased irritability at the synapses (peripherally or in the spinal cord); (4) intensification of the motor outflow by the higher centers (medullary or cerebral); (5) increased sensitiveness or response of the myoneural junctions or nerve ends.

Conceivably, a combination of the presence of an ulcer and a general bodily overirritability of nerves and tissues would produce all these causes. Actually, our clinical studies (outlined below) make it seem probable that the local manifestations not only result from the ulcer but are part of a general preexisting overirritability.

Since we have already assumed that the primary erosion may be produced readily by a variety of agents, the possible causes of general overirritability will be next considered. One may mention the following: (1) alkalosis (diet, administration of alkalis, hyperpnea, loss of gastric secretion, constitution); (2) parathyroid disturbance (parathyroidectomy, functional or organic disease of the parathyroids leading to insufficiency, ductless gland imbalance); (3) toxic agents (from intestinal putrefaction, guanidine salts, ergotoxin, cocaine, caffeine, unknown toxins); (4) disturbance in the calcium metabolism (decreased ionizable calcium in the blood and tissues brought about in various

ways); (5) vegetative nervous system (excessive lability, "imbalance," overirritability of centers, nerves, myoneural junctions or nerve ends; relation to the ductless glands, relation to the hydrogen and other ion balances), and (6) psychic influences (involving the voluntary and involuntary nervous system and ductless glands). These seem to be the most important conditions disposing to an overirritability either in the nervous system or the tissues themselves. It is our intention to investigate in the future these possibilities, both clinically and experimentally. At the present it seems to us more probable that a condition of mild or latent tetany, or a similar condition, or a disturbance of the vegetative nervous system, or a combination of these, may be the general bodily characteristic that interferes with the healing of ulcer.

The following studies, therefore, were made on patients: (1) the response to electrical stimulation (galvanic); (2) the mechanical irritability of muscle and nerve (the "idiomuscular contraction" and Chvostek sign); (3) the amount of total calcium in the blood; (4) the symptoms and signs of disturbance in the vegetative nervous system, and (5) the pharmacologic stimuli of the vegetative nervous system (using epinephrine and atropine). It is proposed eventually to carry out, in addition, the studies given in table 1.

TABLE 1.—*Future Studies*

Capillaroscopy	Sensory thresholds to pain and touch
Reflexes	State of hair, teeth, nails
Habitus	Hydrogen, calcium, phosphorus and chloride concentration in blood
Nonprotein nitrogen bodies in the blood	Alveolar and blood carbon dioxide tension
Familial tendencies	Alkaline tide in urine and blood
Pilocarpine reaction	

The patients selected for the present study were those with ulcer of the stomach or duodenum proved clinically, roentgenographically, and in most cases surgically. Normal subjects and a few symptomless postoperative ulcer cases were included. A number of patients with gastric symptoms, with negative roentgen-ray and surgical findings ("gastric neurosis"), also were observed. The entire group were male adults.

ELECTRICAL IRRITABILITY

Method.—A 1 cm. electrode of the usual galvanic battery was applied to the ulnar nerve between the olecranon and the internal condyle. The cathodal closing current was gradually increased until a perceptible contraction of any innervated muscle was noted. The anodal closing contraction was similarly obtained. Opening contractions under .5 milliamperes were not obtained and currents over this, being too disagreeable to the patients, were not applied. The same apparatus (Wappler) and technic were used throughout.

Studies.—1 Normal controls (male adults) were used and forty patients tested. A current over 3 milliamperes for a cathodal closing contraction was required by 82 per cent.

2. Ulcer patients were used, and sixteen patients tested. Of these 87 per cent reacted to a cathodal closing current under 3 milliamperes.

3. Gastric neurosis was studied, and seven patients tested. Five reacted under 3 milliamperes.

MECHANICAL IRRITABILITY

Method.—The facial nerve was tapped at the ear, over the parotid, and at the zygomatic arch, and the facial, eye and mouth muscles observed for the twitching response (Chvostek's sign). The biceps muscle belly was struck smartly with the finger tip or a small percussion hammer, and the appearance of a lump (so-called idiomuscular contraction) or fibrillary twitchings noted. A positive Chvostek sign with marked lumping or twitching was designated as a strongly positive reaction.

TABLE 2.—*Calcium in the Blood*

		Mg. per 100 Cc.			Mg. per 100 Cc.
1.	Pyloric stenosis, ulcer	10.0	9.	Duodenal ulcer	11.4
2.	Duodenal ulcer	10.0	10.	Duodenal ulcer	10.2
3.	Duodenal ulcer	10.5	11.	Duodenal ulcer	9.0
4.	Duodenal ulcer	10.9	12.	Duodenal ulcer	10.3
5.	Duodenal ulcer	10.0	13.	Duodenal ulcer	10.3
6.	Duodenal ulcer	10.9	14.	Duodenal ulcer	10.7
7.	Duodenal ulcer	10.8	15.	Duodenal ulcer	10.0
8.	Duodenal ulcer	9.3	16.	Duodenal ulcer	11.1

Studies.—Normal controls were used, and eighty patients tested. Sixty-eight, or 85 per cent, were negative. The twelve positive cases were markedly emaciated, miscellaneous postoperative cases.

Twenty-six duodenal ulcer patients were tested. Seventeen, or 65 per cent, reacted strongly, eight, or 30 per cent, moderately, and one was negative.

Eleven gastric ulcer patients were tested. Six reacted strongly and five moderately.

Gastric neurosis was studied, fifteen patients being tested. Ten, or 66 + per cent, were negative, four slightly and one strongly, positive.

TOTAL CALCIUM IN THE BLOOD

Method.—Dr. Lewis T. Mann carried out the Kramer-Tisdall method for determining total calcium in the blood serum of sixteen patients (table 2). The normal concentration of calcium in the blood is from 10 to 11 mg. per hundred cubic centimeters.

DISTURBANCE OF THE VEGETATIVE NERVOUS SYSTEM

Method.—All the symptoms and signs that are associated with abnormal functioning of the vegetative nervous system were systematically looked for (table 3). Cases with several of these signs and symptoms, which were quite obviously instances of a disturbed involuntary nervous system, were considered strongly positive. Because it is as yet undecided whether the gastro-intestinal symptoms are primary or secondary in ulcer, they were disregarded.

Studies.—Duodenal ulcer was studied; twenty-five patients were tested. Twenty-two, or 88 per cent, were negative, two slightly positive, and one strongly positive.

Eleven gastric ulcer patients were studied. Ten were negative, one slightly positive.

Gastric neurosis was studied, nineteen patients being tested. Seventeen, or 89 per cent, were strongly positive, and two were negative.

TABLE 3.—*Vegetative Nervous System Signs and Symptoms*

Miosis, Mydriasis	Aschner reaction
Epiphora, Dryness	Tschermak reaction
Exophthalmos,* Enophthalmos	Atropine reaction*
Narrow fissure, Wide fissure	Epinephrine reaction*
Pallor,* Flushing*	Unrest
Dermographism,* Pigmentation*	Asthma
Salivation,* Dryness*	Cardiospasm, dysphagia
Size of thyroid and tonsils	Mucus colitis, biliary colic
Blood pressure, low* or high	Drug and food idiosyncrasy
Bradycardia,* Tachycardia	Seasonal variation of symptoms*
Respiratory arrhythmia, Palpitation	Libido
Narrow arteries, eosinophilia	Asthenia*
Dry, or cold*, clammy hands	Headache
Hypermotility,* Atony	Dizziness
Constipation,* Diarrhea	Hyperhidrosis*
Loewi reaction	

* Symptoms most frequently encountered.

PHARMACOLOGIC STIMULATION OF THE VEGETATIVE NERVOUS SYSTEM

Method.—1. Epinephrine: 0.5 cc. of a fresh, 1:1,000 epinephrine (adrenalin, Parke, Davis & Co) was given subcutaneously. Blood pressure readings were taken before the injection until a level was maintained and after the injection every minute until the original level was restored. A rise in the systolic pressure of 20 mm. or more, or a small rise (from 10 to 20 mm.) if accompanied by severe general symptoms, was considered a strongly positive reaction.

2. Atropine: Atropine sulphate (1 mg.) was administered subcutaneously and the pulse rate, pupils and symptoms observed for one hour. A rise in the pulse rate of 20 or more with dilated pupils and dryness was considered a strongly positive reaction.

Studies.—(*a*) Normals: Peabody and others [6] in a study of epinephrine sensitiveness found that 14 per cent of normals gave a positive reaction. Kessel and Hyman,[7] while studying these drug reactions in exophthalmic goiter, found that 30 per cent of normal persons react to epinephrine and 22 per cent to atropine.

(*b*) A summary of the patients tested is given in table 4.

COMMENT

Compared to normal persons, patients with gastric or duodenal ulcer tend to respond excessively to various stimuli. A survey of the foregoing studies indicates that from 60 to 80 per cent of the ulcer patients

TABLE 4.—*Summary of Patients Tested*

Disease	Patients	Drug	Reaction			
			Strong	Moderate	Weak	Negative
Duodenal ulcer	15	Epinephrine	5	4	5	1
Duodenal ulcer	11	Atropine	9	2	—	—
Gastric ulcer	8	Epinephrine	5	1	2	—
Gastric ulcer	7	Atropine	6	1	—	—
Cured ulcer	8	Epinephrine	6	1	1	—
Cured ulcer	8	Atropine	8	—	—	—
Gastric neurosis	10	Epinephrine	7	1	1	—
Gastric neurosis	6	Atropine	4	2	—	—

react to small galvanic currents, possess marked nerve and muscle irritability, and give an exaggerated response to epinephrine and atropine.

This study shows, in addition, an almost complete absence of the signs and symptoms of a disturbance of the vegetative nervous system in these patients. Vagotonia and sympathicotonia, or "autonomic imbalance," [7] as definite clinical states, were not encountered. An occasional symptom or sign was found which did not seem enough to distinguish these patients from normal persons. In marked contrast to the ulcer patients, the cases of "gastric neurosis" are practically all outspoken examples of a disturbed vegetative nervous system. They present many or most of the stigmas (table 3). Also they react excessively to electrical and pharmacologic stimulation but only rarely to mechanical stimulation. The relationship of these two groups is not clear. The neuroses do not seem to merge with the ulcer group. We believe that this distinction may prove of great value clinically in differentiating ulcer from neurosis. In fact, it has been possible recently to predict correctly the operative findings in a few doubtful cases. This clinical application is now being actively investigated.

6. Peabody, F. W.; Sturgis, C. C.; Tompkins, E. M., and Wearn, J. T.: Am. J. M. Sc. **161**:508 (April) 1921.

7. Kessel, L., and Hyman, H. T.: Am. J. M. Sc. **165**:513 (April) 1923.

It may be suggested that the general overirritability is the result of the lesion and not the underlying cause of the chronicity. To decide this it will be necessary to observe patients with ulcer symptoms, and later the same patients when cured, preferably surgically. To date we have studied only four such cases; they presented, while well, the same signs of overirritation. We have also studied eight cases in which ulcers were removed surgically. The symptoms were relieved, but the overirritable condition was nevertheless still present. It would be of interest in this connection to see whether the few ulcer patients with little or no overirritability heal or lose their symptoms more promptly.

We do not know as yet the explanation of the overirritability. It seems to be closely related to both tetany and the vegetative nervous system. With reference to tetany, it may be said that this condition in its various forms presents a perplexing problem. It appears that the parathyroids, certain toxins and the ion balance in the blood and tissues probably are all involved. We found normal total calcium figures in the blood, but tetany may occur with normal calcium figures. It is agreed that the disturbance is in the ionizable calcium and we have no method of estimating this at present. The involvement of the vegetative nervous system in tetany as well as its functional disturbances in general also are complex problems. Although it is well known that the parasympathetic and sympathetic may be imbalanced, or both may respond excessively to stimuli, the explanation of such states is as yet unknown.

In general, it is our impression that a mild or a latent tetany, or a closely related state, with a secondary involvement of the vegetative nervous system, is the underlying cause of the failure to heal in ulcer of the stomach or duodenum. Whether it depends ultimately on a parathyroid disturbance cannot be answered in the present state of our knowledge. Experimental work on animals is now being carried on in the surgical laboratories of the Columbia University College of Physicians and Surgeons in which the effect of such general disturbances as mentioned here on the rate of healing of artificially induced gastric mucosal defects is being studied.

SUMMARY

1. Superficial ulcers or erosions of the stomach or duodenum occur owing to various local and general causes, but heal perfectly in most persons.

2. In certain subjects the lesion progresses and takes on the features of chronicity. This is the characteristic of ulcer as a disease entity.

3. The usual explanations, mostly referable to local conditions, for the failure to heal seem incomplete. It is suggested that some general bodily condition, interfering with the physiology of healing, may be present.

4. An excessive response to stimuli on the part of the nerves and tissues, locally or generally, may furnish such interference to healing. Tetany or a related condition, a disturbance of the vegetative nervous system, or a combination of both, are possible causes of the supposed general overirritability.

5. Patients with ulcer, with gastric neurosis, and controls were tested with various stimuli to ascertain the presence of such overirritable states.

6. Almost all the ulcer patients respond excessively to mechanical, electrical and pharmacologic stimulation. Patients with gastric neurosis react similarly, except to mechanical stimuli, but present a marked contrast to the ulcer group in that they display obvious stigmas of a disturbed vegetative nervous system. This distinction may prove useful clinically.

7. The persistence of the overirritability after a surgical cure suggests that it is a general bodily state, probably constitutional, and not merely the result of the presence of the ulcer.

THE THERAPEUTIC USE OF DIETS LOW IN WATER AND IN MINERAL CONTENT*

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The importance of a diet low in chlorides for certain cases of nephritic edema was demonstrated by Widal[1] in 1903. In his cases chlorides were readily retained, but equal retention of water was not shown. The ingestion of a diet low in chlorides was followed by diuresis and loss of edema. In our experience, in cases of obstinate edema due to renal disease inability to excrete both chlorides and water usually was manifested and thus the so-called salt-free diet failed to produce diuresis and loss of edema. While considering possible dietetic reasons for this failure, we found by analysis that our routine salt-free diet contained a small quantity of chloride, from 2 to 3 Gm., but from 1,200 to 1,400 cc. of water. This amount of water when added to that ingested as fluid, from 600 to 1,000 cc., made the daily intake from 1,800 to 2,400 cc. In revising the diet we hoped (1) to decrease the water contained; (2) to reduce the amount of sodium, since sodium retention has been shown to be associated with water retention, and (3) so to control the diet that this minimal content of water and mineral would be, for practical purposes, the same from day to day. Such a diet has been used in the wards of St. Mary's Hospital for the last two years and has proved a most effective adjunct in the treatment not only of cases of obstinate edema due to nephritis but also of those of persistent ascites due to hepatic and cardiac disease. The object of this paper is to show that the administration of such a diet is a useful therapeutic measure, that important quantitative data can be thus obtained and that after its continuation for several months there is no apparent evidence of diet deficiency.

COMPOSITION OF THE DIETS

Type of Food.—When a patient with nephritis enters the hospital he is placed on a diet calculated to meet the basal requirements of the average adult. Such a diet contains 40 Gm. of protein and 1,500 calories. Basal diets for patients with nephritis in the department of medicine at St. Mary's Hospital are planned on a foundation diet con-

* From the division of medicine, Mayo Clinc.

1. Widal, F., and Javal, A.: La cure de déchlorination; son action sur l'oedème, sur l'hydratation et sur l'albuminurie à certaines périodes de la néphrite épithéliale, Bull. et mém. Soc. méd. d. hôp. de Paris **20**:733-749, 1903.

taining 800 Gm. of fruits and vegetables, 100 Gm. of bread and 20 Gm. of dry cereal. This basis contains approximately 20 Gm. of protein. To this is added food containing complete proteins to make up the required 40 Gm., and carbohydrates and fats to produce 1,500 calories. These diets contain between 1,200 and 1,400 Gm. of water as calculated from the percentage composition of water in the foods served. Diet 1, table 1, shows the mineral content of the basal diet for patients with nephritis. This is our routine salt-free diet. To make it more palatable for patients who have nephritis without edema, 5 Gm. of extra salt was added during the process of preparation.

Because these diets contained considerably more water than we had anticipated, they were first modified by lowering the water content of the food. Eight hundred grams of water was the standard accepted. Foods with a low water content were selected and a diet formulated which contained 40 Gm. of protein, 1,500 calories. Later the mineral content of the food was calculated. It was found to be rather uniformly low in all mineral salts except those of potassium. This was high, as

TABLE 1.—*Composition of the Diet*

Diet	Carbohydrate, Gm.	Protein, Gm.	Fat, Gm.	Calories	Water, Cc.	Sodium, Gm.	Potassium, Gm.	Calcium, Gm.	Magnesium, Gm.	Chlorine, Gm.	Phosphorus, Gm.	Sulphur, Gm.	Iron, Gm.
1	189	37	65	1,531	1,286	1.156	3.745	0.807	0.312	1.585	0.991	0.736	0.013
2	148	40	80	1,515	809	0.507	1.625	0.225	0.196	0.668	0.657	0.562	0.009
3	243	40	92	2,016	834	0.528	1.637	0.328	0.212	0.693	0.666	0.569	0.009
4	175	50	126	2,094	872	0.747	1.772	0.292	0.308	0.867	0.741	0.692	0.011
5	235	50	144	2,508	895	0.770	1.872	0.307	0.223	0.888	0.751	0.700	0.011

potato had been used in generous amounts because of its high carbohydrate content. Rice or macaroni was then substituted for the potato in the diet, and the potassium content was reduced considerably (diet 2, table 1). This diet contains 600 Gm. of fruits and vegetables. No evidence of deficiency of mineral or vitamin has appeared in patients who have been on this diet for several months. In selecting foods to fill the diet prescription we made an attempt to secure foods that would be available for a long period of time in order that the diet might be held constant. Fresh fruits and vegetables were used whenever possible. At least 400 Gm. of the amount allowed was served as fresh fruit and green vegetables. Orange, grapefruit, banana, lettuce, tomato and string beans were used. Canned tomatoes and canned string beans also were used, standard brands having been selected for analysis. All food was prepared and served without extra salt. The foods served were weighed and the uneaten portions were reweighed. A permanent record of the diet actually eaten was calculated and charted. The actual fluid ingested over and above that in the food was from 600 to 800 cc. daily, making the total fluid intake from 1,400 to 1,600 cc.

After the caloric requirement and the ability of the patient to use protein food had been determined, the diet was adjusted to meet the actual requirements of the individual. This necessitated the calculation of several standard diets. An attempt was made to hold the water and mineral content as nearly constant as possible while the protein and calories were increased (diets 3, 4 and 5, table 1). Two thousand calories, diet 3, was suitable for a group of patients who were able to be up and required about 30 per cent more than their basal calories, without an increase in protein allowance, the increased fat and carbohydrate acting as sparers of body protein. Diet 4 (table 1) was calculated for the patient needing 50 Gm. of protein daily. Diet 5 (table 1) shows the increase in water and minerals necessary to allow the patient 50 Gm. of

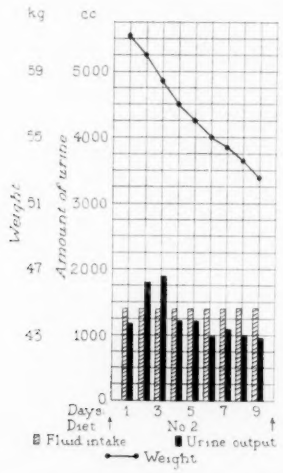

Chart 1 (case 1).—Findings in chronic nephrosis.

protein and 2,500 calories daily. As the protein and calories in the diets increased over the basal, a slight increase in water and mineral content occurred. Calories were increased by adding sugar and fat. Egg and milk protein were used to increase the protein content of diets 4 and 5.

A number of menus for varying the methods of preparing and serving the diets were planned. Patients were taught how to prepare these diets at home, and each was provided with a pair of gram food scales and instructed in their use. Quantitative diet sheets were written for these patients and lists of substitutions provided for everyday use. Food values and diet calculation were taught to the patient or to some member of his family but, with a diet holding thirteen factors constant, the variety of food is necessarily limited. These patients have been

successful in following instructions at home and have become adjusted to the dietary limitations. Table 2 gives the quantities of the individual articles of food for a single day.

Chemical Content.—Analysis of the water and mineral content of the particular foods served in the weighed low salt, low fluid diet (diet 2) was undertaken because of the significance the minerals are believed to have in the dietary treatment of the cases described; also to determine whether analysis with the newer micro methods would yield data that would corroborate the results obtained by previous workers, especially those used by Sherman [2] in his tables. It was believed that should the methods used by us for mineral analysis give results reasonably close to the accepted standards for the mineral content of foods such as Sherman has compiled, we would be justified in using them for purposes of calculation.

In table 3, Sherman's figures and our data are compared. In most cases the two are remarkably close, but nearly every food shows varia-

TABLE 2.—*Weighed Low Salt, Low Fluid Diet (Dict 2, Table 1)*

Breakfast	Gm.	Dinner	Gm.	Supper	Gm.
Ten per cent fruit	100	Five per cent vegetable	100	Five per cent vegetable	100
Eggs (one)		Rice	100	Macaroni	100
Toast	20	Banana	100	Fifteen per cent fruit	100
Butter	10	Meat	45	Ten per cent fruit	100
Sugar	5	Mayonnaise	15	Bread	20
		Bread	20	Butter	15
		Butter	15	Eggs (one)	
		Sugar	5	Mayonnaise	15
				Sugar	5

tion, sometimes to a considerable extent in one or more of the minerals. The greatest differences occurred in the case of dried fruits. Discrepancies in these foods were not unexpected because the manner of drying and the degree to which they are dried offer considerable chances of error. Hence, whenever possible these foods are not included in diets served during periods when accurate studies are being made.

For studies such as those reported here, in which no special attempt has been made to determine with great accuracy the mineral balance, the use of standard figures for purposes of calculating the approximate daily intake of mineral and water seems justifiable.

Determinations of the inorganic acid and basic ions, urea nitrogen, ammonia nitrogen and total nitrogen of the urine were made in two normal persons and two patients with edema and ascites who were receiving diets 2 or 4. Daily estimations were made during the four experiments and listed for the two patients, but only the values of the first

2. Sherman, H. C., and Gettler, A. O.: The Balance of Acid-Forming and Base-Forming Elements in Foods, and Its Relation to Ammonia Metabolism, J. Biol. Chem. **11**:323-338, 1912.

and last day of the two normal controls are given. The daily inorganic and nitrogen content of the diet also is given (table 4). This table shows the decrease in the excretion of the inorganic salts and ions which occurs when a normal person changes from an ordinary mixed diet to one low in mineral content. On the fifth day of experiment with subject 6 and on the third day of experiment with subject 5 the total nitrogen of the urine approximates that in the diet. Similar nitrogen values were obtained in case 1. In the normal controls the output of chlorine and sodium reached values close to those of the dietary intake on the third and fifth days, respectively.

The results obtained in cases 7 and 1 are included to show by contrast how the daily urine excretion of chlorine and sodium in abnormal cases continued to be persistently higher than the intake. This excess excretion of chlorine and sodium is due in part to the abnormal storage

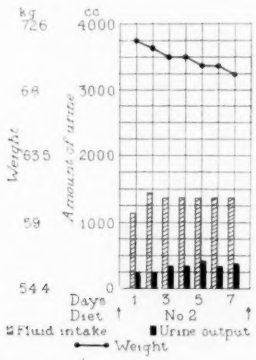

Chart 2 (case 2).—Findings in Banti's disease with ascites.

of these ions in the tissues of these patients. Such a continued net loss of chlorine and sodium also emphasizes the therapeutic value of the diet.

USE OF THE DIETS

Up to the present we have used the low salt, low fluid diet in eight cases of subacute or chronic nephritis with marked edema and twenty-five cases of chronic ascites with liver diseases or with liver disease and cardiac insufficiency. In many of these cases satisfactory diuresis was produced by the combined use of the diet, ammonium chloride and novasurol.[3] In a case of chronic nephrosis (case 1, table 4, chart 1) spon-

3. Keith, N. M.; Barrier, C. W., and Whelan, Mary: The Diuretic Action of Ammonium Chloride and Novasurol in Cases of Nephritis with Edema, J. A. M. A. **85**:799-806 (Sept. 12) 1925. Rowntree, L. G.; Keith, N. M., and Barrier, C. W.: Novasurol in the Treatment of Ascites in Hepatic Disease, J. A. M. A. **85**:1187-1193 (Oct. 17) 1925.

TABLE 3.—*Food Analysis*

Food	Water, Grams per Cent		Sodium, Grams per Cent		Potassium, Grams per Cent		Calcium, Grams per Cent		Magnesium, Grams per Cent		Chlorine, Grams per Cent	
	Clinic	Atwater and Bryant [4]	Clinic	Sherman	Clinic	Sherman	Clinic	Sherman	Clinic	Sherman	Clinic	Sherman
Orange	86.8	86.9	0.0138	0.012	0.156	0.177	0.021	0.045	0.008	0.012	0.008	0.006
Orange juice	85.9	....	0.009	0.008	0.200	0.182	0.015	0.029	0.014	0.011	.....	0.003
Grapefruit	90.8	....	0.006	0.004	0.164	0.161	0.010	0.021	0.007	0.009	0.009	0.005
Banana	72.0	75.3	0.030	0.034	0.408	0.401	0.006	0.009	0.028	0.028	0.126	0.125
Apple	85.9	84.6	0.015	0.011	0.123	0.127	0.117	0.007	0.006	0.008	0.037	0.005
Beans	94.3	93.7	0.015	0.019	0.160	0.247	0.052	0.046	0.019	0.025	.....	0.024
Lettuce	96.2	94.7	0.0272	0.027	0.209	0.329	0.028	0.043	0.011	0.017	0.056	0.074
Tomato	92.0	94.3	0.224	0.010	0.280	0.275	0.006	0.011	0.011	0.010	0.058	0.034
Potato	74.3	75.5	0.018	0.021	0.501	0.429	0.005	0.014	0.019	0.028	0.027	0.038
Rice	70.6	72.5	0.012	0.025	0.046	0.070	0.020	0.009	0.033	0.033	0.056	0.054
Macaroni	76.6	78.4	0.0095	0.008	0 054	0.130	0.036	0.022	0.038	0.037	0.077	0.073
Bread, salted	29.7	35.6	0.517	0.394	0.110	0.108	0.040	0.027	0.028	0.023	1.09	0.607
Bread, salt free	40.3	35.6	0.067	0.394	0.070	0.108	0.016	0.027	0.013	0.023	0.116	0.607
Bread, whole wheat, salt free	....	38.4	0.034	.....	0.108	.....	0.011	.....	0.039	.....	0.031	.....
Steak, porterhouse	47.0	52.4	0.409	0.067	0.402	0.271	0.006	0.009	0.025	0.018	0.045	0.060
Egg white	84.7	86.2	0.190	0.156	0.137	0.160	0.012	0.015	0.012	0.010	0.163	0.155
Egg yolk	50.1	49.5	0.114	0.075	0.109	0.115	0.125	0.137	0.014	0.016	0.050	0.166
Butter, salted	35.0	....	0.929	0.788	0.019	0.014	0.016	0.015	0.002	0.001	0.935	1.212
Butter, salt free	....	....	0.009	.....	0.004	0.014	0.015	0.015	0.050	0.001	0.162	.....
Salad dressing	7.6	....	0.041	.....	0.008	.....	0.009	.....	0.002	.....	0.056	.....
Sugar	0.0	....	0.001	.....	0.004	.....	0.008	.....	0.003	.....	0.033	.....
Fig	14.0	18.8	0.081	0.046	0.647	0.964	0.143	0.162	0.054	0.071	0.198	0.043
			0.072		0.742		0.180		0.058			
			0.076		0.694		0.161		0.056			
Raisin	22.0	14.6	0.099	0.133	0.648	0.820	0.023	0.064	0.025	0 083	0.066	0.082
			0.103		0.909		0.063		0.044			
			0.101		0.799		0.043		0.034			
Date	16.7	15.4	0.049	0.055	0.611	0.034	0.065	0.047	0.069	0.069	0.268	0.228
			0.048		0.490		0.037		0.046			
			0.049		0.500		0.035		0.046			

TABLE 4.—*Comparison of Intake in Food and Output in Urine*

Case	Age	Sex	Diet	Date, 1925	Urine, Cc.	Chlorine, Gm.		Sulphur, Calculated as SO_3, Gm.		Phosphorus, Gm.		Sodium, Gm.		Potassium, Gm.		Calcium, Gm.		Magnesium, Gm.		Ammonium Nitrogen, Gm.	Urea Nitrogen, Gm.	Total Nitrogen, Gm.		Diagnosis
						Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	Intake	Output	Output	Output	Intake	Output	
5	29	M	4	6/23	500	0.87	2.33	1.698	1.22	0.741	0.495	0.747	1.61	1.772	1.25	0.292	0.16	0.208	0.085	0.365	6.1	8.0	7.6	Control
				6/25	450	....	0.86	.....	1.15	....	0.662	....	0.35	.....	1.33	.....	0.18	.....	0.120	0.396	6.1	...	8.6	
6	29	M	2	4/28	975	0.67	3.68	1.405	.....	0.66	0.76	0.51	2.22	1.62	2.28	0.23	0.144	0.20	0.092	0.36	8.09	6.4	9.6	Control
				5/ 2	425	....	0.61	.....	.....	....	0.49	....	0.44	....	1.92	....	0.092	....	0.093	0.23	....	...	6.9	
7	36	M	2	9/ 1	700	0.67	2.77	1.405	0.182	0.66	0.336	0.51	1.89	1.62	1.23	0.23	.....	0.20	.....	.....	.....	6.4	...	Portal cirrhosis with ascites
				9/ 2	1,300	....	3.02	.....	0.180	....	0.444	....	2.26	....	1.51	....	.....	.....	.....	0.492	....	...	...	
				9/ 3	900	....	2.16	.....	0.783	....	0.369	....	1.71	....	1.17	....	.....	.....	.....	.....	....	...	...	
				9/ 4	700	....	2.02	.....	0.728	....	0.413	....	1.94	....	1.02	....	.....	.....	.....	0.210	....	...	...	
1	48	F	2	5/22	1,150	0.67	4.32	1.405	.....	0.66	0.322	0.51	2.76	1.62	1.43	0.23	0 018	0.20	0.061	0.288	3.76	6.4	6.4	Chronic nephrosis
				5/23	1,800	....	5.40	.....	0.396	....	0.486	....	3.98	....	1.78	....	0.015	....	0.074	0.738	5.73	...	7.5	
				5/24	1,850	....	5.34	.....	0.229	....	0.420	....	2.77	....	1.52	....	0.009	....	0.074	0.352	4.83	...	6.3	
				5/25	1,200	....	3.67	.....	0.341	....	0.396	....	1.20	....	1.24	....	0.011	....	0.052	0.214	3.36	...	6.1	
				5/26	1,200	....	3.67	.....	0.342	....	0.432	....	2.22	....	1.36	....	0.017	....	0.048	0.240	3.53	...	6.3	
				5/27	950	....	3.20	.....	0.391	....	0.390	....	2.15	....	1.18	....	0.011	....	0.036	0.257	2.22	...	5.2	
				5/28	1,050	....	2.70	.....	0.311	....	0.420	....	1.94	....	1.23	....	0.011	....	0.041	0.284	3.15	...	5.9	

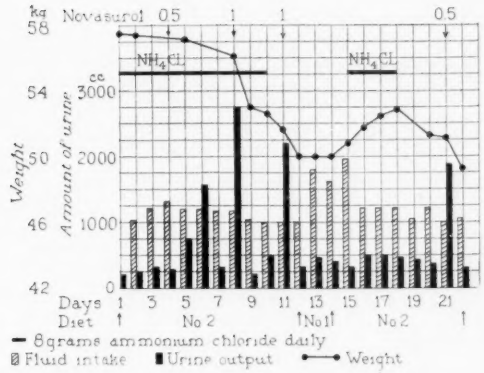

Chart 3 (case 3).—Findings in chronic nephrosis.

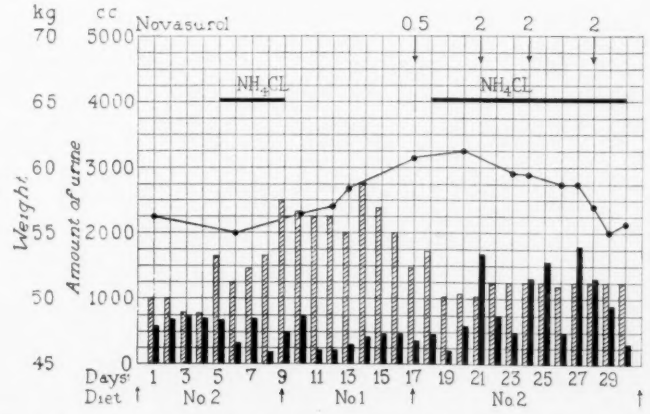

Chart 4 (case 4).—Findings in polycythemia with ascites: heavy horizontal line, from 36 to 72 Gm. of ammonium chloride; curve, weight; shaded columns, fluid intake; solid columns, urine output.

taneous diuresis and loss of edema occurred and body weight decreased 8.5 Kg. on the diet alone. Later it was found necessary to use novasurol and ammonium chloride to reduce the marked edema further. Similarly, in a case of Banti's disease with ascites the patient lost 2 Kg. in body weight in seven days on the diet alone (chart 2).

Two patients undergoing the combined treatment found this diet difficult to take so the salt and water content was increased; there was a rapid retention of fluid and gain in weight. One of these, a patient with chronic nephrosis (case 3, chart 3), was finally able to take the low salt, low fluid diet regularly and the combined treatment produced the desired effects. We had a similar experience in a case of ascites (case 4, chart 4).

Several of our patients have found it necessary to remain on this diet for a period of three months and no ill effects have been noted. The patients' adherence to the diet is of interest for they soon realize from experience that if the intake of water and salt is increased beyond their tolerance an increased retention of fluid and a gain in weight occurs.

SUMMARY

Carefully controlled diets of low mineral and water content are both practicable and effective in the treatment of cases of edema and ascites. The diets may be varied in protein and caloric value with little increase in mineral or water content.[4] There have been no demonstrable ill effects from the continued use of these diets.

4. Atwater, W. O., and Bryant, A. P.: The Chemical Composition of American Food Materials, ed. 3, United States Department of Agriculture, Office of Experimental Station, Bull. 28, Washington, Government Printing Office, 1906.

WATER METABOLISM

II. FURTHER OBSERVATIONS *

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In a previous article [1] it was reported that the amount of water that it was possible to cause a dog to excrete by the intravenous injection of glucose was directly proportional to the alkalinity of the blood as measured by the carbon dioxide combining power of the plasma (Van Slyke). The level of carbon dioxide of 45 is the critical point and if the dog is below that level of alkalinity, dehydration by glucose injections is impossible, all the water being "fixed" by the colloids or at least being in a relatively firm combination with the colloids. Above that level, an increasingly large amount is held in a freer or looser combination, and this "free" water acts as a body reserve.

A continuation of these studies, using hypertonic salt solution as the dehydrating agent, has yielded similar results. Dogs were injected intravenously with a 5 per cent solution of sodium chloride at the rate of 25 cc. per kilogram. The injections were made with a Woodyatt pump and planned to consume ninety minutes. A catheter was introduced into the dog's bladder and the flow of urine measured. In this set of experiments the onset of the diuresis was less prompt than in the previously reported glucose dehydrations. The injections were continued for from seventy to ninety minutes before the urine excreted exceeded the water injected. The length of time before the flow of urine ceased was from three and a half to four hours. In general sodium chloride proved to be a more powerful diuretic than glucose. In other words it was possible to wring water from the tissues at lower levels of alkalinity. This is in line with our knowledge of the behavior of colloid-water combinations in vitro. The experiment given in table 1 is illustrative of the method.

If the results of the previously reported glucose dehydrations are plotted the curve of chart 1 results. It will be noticed that the results are not strictly quantitative. This is undoubtedly owing to the fact that the sugar metabolism of the dog is not a constant factor. Slight variations in the glycogen reserve of the liver, in the general nutrition of the animal, as well as the functional capacity of the pancreas have just enough influence to make the curve slightly irregular.

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* From the department of surgery, University of Illinois College of Medicine.

1. Andrews, Edmund: Water Metabolism, Arch. Int. Med. **37**:821 (Jan.) 1926.

In these salt solution dehydrations, I was quite astonished when plotting the curve to note that when the points were laid on the chart it was possible to draw a line through them with a ruler. In this case no metabolic elements entered into the equation. The mathematical accuracy of the results can be interpreted only as a confirmation of the theory that in these water problems we are dealing solely with physicochemical forces, and that no "vital" or "life" factors are acting. The results are comparable in accuracy with those achieved in ordinary chemical work on colloids.

TABLE 1.—*Experiment 36*

Male dog, weighing 9 Kg., injected with 330 cc. of 5 per cent sodium chloride at a constant rate during ninety minutes; carbon dioxide, 46.7.

Time	Intake	Output	Loss	Loss per Kg.
10:35 injection begun				
10:50	55	10	...	..
11:05	110	70	...	..
11:20	165	140	...	..
11:35	220	220	...	..
11:50	275	320	45	4
12:05 injection stopped	330	520	190	21
12:20	330	600	270	30
12:35	330	650	320	35
1:05	330	680	350	39
1:15	330	700	370	41
1:30	330	720	390	43
2:00	330	735	405	45

This dog, therefore, whose carbon dioxide was 46.7 was dehydrated to the extent of 45 cc. per kilogram.

Table 2 shows the results of a series of such experiments.

TABLE 2.—*Results in Series of Experiments*

Experiment	Carbon Dioxide	p_H	Water Loss
40	53.0	7.45	40
43	52.4	7.40	42
28	49.4	....	60
32	48.0	....	55
29	47.5	....	50
36	46.7	....	45
38	44.3	7.40	36
30	42.3	....	26
34	40.8	....	22
42	36.8	7.25	4.5

It will be noted that in each curve there is a drop in the amount of free water as we reach the extreme alkaline end of the scale. This is also strictly in line with our knowledge of the behavior of proteins in vitro.

Hydrogen ion estimations (table 2) were made in some cases and were found to run parallel in a general way. The method used (colorimetric) is not accurate enough to fall within the margin of error in these studies and therefore no exact correspondence is to be expected.

CONCLUSIONS

1. The amount of "free" water in the tissues varies with the alkalinity of the blood as measured by the carbon dioxide combining power of the plasma.

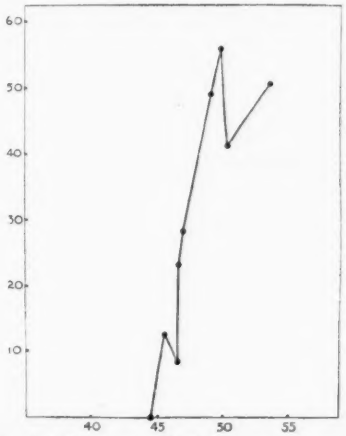

Chart 1.—Glucose dehydrations: abscissas, cubic centimeters of water lost; ordinates, carbon dioxide (Van Slyke).

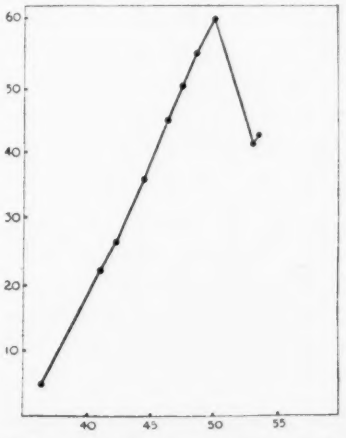

Chart 2.—Salt solution dehydrations: abscissas, cubic centimeters of water lost; ordinates, carbon dioxide (Van Slyke).

2. The exact mathematical accuracy of this proportion, when hypertonic salt solution is used as the dehydrating agent, is evidence that the elimination of water in these experiments is purely a physicochemical phenomenon and that no "vital" factors need be considered.

THE EFFECT OF DIGITALIS ON VENTRICULAR PREMATURE CONTRACTIONS *

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In a recent article by one of us [1] attention is called to the errors arising from theoretic deductions on the effect of digitalis in disorders of cardiac rhythm. Without a more exact understanding of the precise manner in which digitalis in varying doses affects the different cardiac functions, and also without a clearer understanding of the precise mechanism producing the different disorders of rhythm, it is necessary, in order to ascertain the response to digitalis, to investigate each arrhythmia directly. It is a matter of common experience to observe premature contractions, particularly of the ventricular type, called forth by digitalis. The ventricular premature contraction is especially common in patients with auricular fibrillation. In some of the latter, large doses are necessary; in others, rather small doses are sufficient to produce them.

Our knowledge of the effect of digitalis on premature contractions occurring spontaneously is not quite so definite. In 1911 Edens [2] recorded the impression that the behavior of premature contractions toward digitalis depends on the cause that produces them. Thus he found that in a patient with premature contractions during the course of an attack of acute rheumatic fever digitalis had no effect. Likewise, in patients in whom smoking was the etiologic factor digitalis was without influence on the frequency of the premature contractions. However, he stated that he observed digitalis influenced favorably a tendency to the production of premature contractions in a number of patients with both normal and decompensated hearts. Wenckebach [3] stated that he cured (?) a number of patients with troublesome premature contractions in diseased as well as in perfectly healthy hearts by "very small doses of digitalis only." He explained the effect of the

* From the third (New York University) medical division and adult cardiac clinic of Bellevue Hospital, and the department of pharmacology, Cornell University Medical College.

1. Gold, H.: Action of Digitalis in the Presence of Coronary Obstruction, Arch. Int. Med. **35**:482 (April) 1925.

2. Edens, E.: Ueber Digitaliswirkung, Deutsches Arch. f. klin. Med. **104**: 512, 1911.

3. Wenckebach, K. F.: The Effects of Digitalis on the Human Heart, Brit. M. J. **2**:1600, 1910.

small dose as a depression of the irritability of the myocardium contrary to the effect of large doses that increase the irritability of the myocardium and give rise to premature contractions. Edens and Huber [4] reported a case of bigeminy of the auricular type with a normal basic rhythm in which a regular rhythm followed the administration of digitalis. They were able to find only two other cases in the literature; one, reported by Wenckebach, of the ventricular type, and the other, reported by Hering, of a character not determined. Mackenzie [5] believed that the cessation of premature contractions under digitalis was independent of the drug and that when the premature contractions had persisted for months or years no form of treatment seemed to abolish them. Christian [6] stated that the relation of digitalis to premature contractions was not established and added that their presence could be neglected in considering the probable efficiency of digitalis therapy.

It is obvious that the few clinical observations recorded on the effect of digitalis on premature contractions are contradictory and, on the whole, unsatisfactory. This is probably due in part to the inherent difficulties attending a thorough investigation of the subject. Premature contractions frequently occur in patients whose hearts are otherwise normal. These patients do not ordinarily apply for treatment, and when they do they are rarely kept in the hospital for the length of time necessary to control properly their reaction to the drug. Furthermore, premature contractions occurring spontaneously show considerable variation in their frequency in the same patient at different times during the day and under different conditions, and for intervals of days or weeks may disappear without any treatment. This inconstancy necessitates long periods of control, the absence of which in the records of most of the earlier experiments has rendered the evidence inconclusive.

For some time we have been pursuing a study of the effects of various drugs on premature contractions. In the course of our work we have been able to complete observations on one patient with premature contractions the results of which answer conclusively a question to which there has not been a definite answer in the literature. Whereas it is known that in some patients large doses of digitalis can produce premature contractions of ventricular origin, can large doses cause the disappearanc of premature contractions occurring spontaneously? This article is a report of the method employed and the results obtained in the observations on this patient relevant to this question.

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4. Edens, E., and Huber, J. E.: Ueber Digitalisbigeminie, Deutsches Arch. f. klin. Med. **118**:476, 1916.

5. Mackenzie, J.: Diseases of the Heart, 1913, p. 202.

6. Christian, H. A.: The Use of Digitalis in Various Forms of Cardiac Arrhythmia, Boston M. & S. J. **173**:306, 1915.

REPORT OF CASE

History.—A man, aged 56, a brass finisher by trade, had had no childhood diseases except measles. He had had rheumatism at the age of 43. He stated that he had had no venereal diseases. The bowels were regular. He had smoked three pipes daily for the last twenty years and took two cups of coffee daily but no tea. Before prohibition he occasionally drank whisky and was intoxicated about once a year. He had not noticed any relation between his present complaints and his smoking, coffee or alcohol. In the previous three years he had been treated several times for sleeplessness and palpitation. Nervousness always aggravated the symptoms. He came to the clinic because of a "jumping heart," dull pain in the precordium and sleeplessness.

Physical Examination.—The patient was well nourished, weighing 160 pounds (72.6 Kg.). There was no evidence of infection from teeth or tonsils. The lungs were negative. The abdomen was negative; the liver and spleen were not palpable. There was moderate sclerosis of the brachial and temporal arteries. There was no edema. The apex beat was visible and palpable in the fifth space, 11 cm. from the midline. The sounds were of good quality. There was considerable accentuation of the second aortic sound. There were no murmurs. The ventricular rate was from 70 to 80 per minute with a pulse deficit of from 10 to 15 beats. The electrocardiogram showed a basic sinus rhythm interrupted by frequent premature ventricular contractions. The temperature was normal. The urine and the blood were normal. The blood pressure varied from 200 systolic, 120 diastolic to 190 systolic, 90 diastolic.

The diagnosis was arteriosclerosis, hypertension, enlarged heart and premature contractions.

Treatment.—The patient was admitted to the hospital and put to bed. Electrocardiograms of five minutes' duration on a preferred lead (Lead I in this case) were taken on bromide paper three times daily, at approximately 9 a. m., 1 and 5 p. m. On days of rapid digitalization these electrocardiograms were taken every hour during the day. When, as occasionally happened, electrocardiography was not available, the ventricular rate was counted for 500 consecutive beats, the premature contractions being recorded as they occurred. After the twenty-seventh day of observation the patient was discharged from the hospital and one such tracing was taken three times a week to keep record of the prevailing rhythm and number of premature contractions. On occasions of repetition of full digitalization three records were taken the day before, a record every two hours on the day of administration, and three records the day following the administration of the digitalis.

Analysis of Chart.—The results obtained are given in the accompanying chart. Curve B is plotted from the average number of premature contractions per minute of each record. It shows clearly the extraordinary variations in the number of premature contractions at different times of the same day and of different days. For instance, at noon of the second day there were eighteen premature beats per minute, whereas at 5 p. m. of the same day there were only four premature beats per minute. Had any drug been administered in the morning one could easily have fallen into the error of assuming it to be the cause of the marked reduction in the number of premature beats.

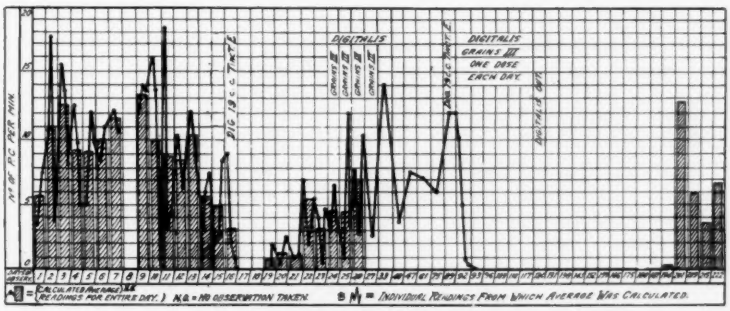
The shaded areas, *A*, of the chart indicate the calculated average number of premature beats per minute for each day, based on the three daily electrocardiograms.

The first control period lasted fifteen days with the premature contractions ranging between five and thirteen per minute daily. On the sixteenth day, 19 cc. of tincture of digitalis with a strength of 1 cc. to the cat unit was given by mouth in one dose at 9:30 a. m. after the first electrocardiogram was taken. The curve shows the continuous diminution in the number of premature contractions during the day. Five hours after this full dose of digitalis the electrocardiogram

showed no premature contractions for the first time in fifteen days of observation, during which period forty-five electrocardiograms of five minutes each were taken.

For two days following the first full dose there were no premature beats. They began to reappear in small numbers on the third day (day 19). Eight days after the first full dose, 3 grains (0.19 Gm.) daily of the powdered digitalis leaf was administered for four days. These smaller doses of digitalis failed to abolish the premature beats. However, from the time of the digitalis administration the number of premature beats was considerably less than for any similar period previously.

Then for a period of fifty-nine days (from day 33 to day 92) no digitalis was given. The premature contractions returned practically to the same range as in the first control period, from four to fourteen per minute daily. On day 92 the patient again received 19 cc. of the same tincture of digitalis employed previously. The number of premature beats began to diminish gradually and seven hours after this full dose of digitalis they had completely disappeared.


DIGITALIS
GRAINS III
ONE DOSE
EACH DAY.
DIGITALIS GRAINS III
DIGITALIS GRAINS III
DIGITALIS GRAINS III

Since there was no evidence of circulatory failure in this patient the disappearance of the premature contractions was not accompanied by any subjective or objective evidence of improved circulation. There was no change in the blood pressure. The annoying sensation of "jumping of the heart" disappeared in the absence of the premature contractions.

PRESSURE ON THE CENTRAL NERVOUS SYSTEM IN ITS RELATION TO HYPERGLYCEMIA: CHRONIC PIQÛRE *

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AND
CAROLINE CROWELL
PHILADELPHIA

Claude Bernard's piqûre [1] showing the close relation of the central nervous system to carbohydrate metabolism attracted the attention of many investigators and clinicians, so that cases of transient glycosuria as well as even cases of diabetes mellitus were examined for changes in the central nervous system. Since it was found that cases of tumors of the central nervous system and also cases of recent cerebral and subdural (intracranial) hemorrhages are often associated with glycosuria, special attention was paid to cases showing symptoms of direct pressure on the medulla oblongata. Indeed, tumors of its own or neighboring tissues, blood extravasations in its immediate vicinity or even into the fourth ventricle, and echinococcus situated occasionally in the cavity of the fourth ventricle have furnished useful anatomopathologic material, suggesting strongly a possible interrelationship between the glycosuria and the pathologic findings in or near the medulla.

The accompanying table includes the cases compiled from the meager literature on this subject. Since blood sugar, the subject under investigation in the present work, has been analyzed in pertinent cases only by recent workers, the table also contains those cases, taken chiefly from old publications, in which the urine only was examined for sugar content. This seems justifiable since, with few exceptions, glycosuria is secondary to a primary hyperglycemia. There also are added a few cases in which the sugar content of the cerebrospinal fluid has been estimated and a hyperglycorrhachia reported. A relation between the sugar level of blood and cerebrospinal fluid has been suggested and demonstrated on clinical material by Thalhimer and Updegraff; [2] the same point of view is upheld by Dopter [3] and by Polonovski and Duhot.[4] Moates and Keegan,[5] experimenting on cerebrospinal

* From the department of physiology, University of Pennsylvania.

1. Bernard: Leçons de Physiologie Experimentale, Paris, 1855, p. 309.
2. Thalhimer, W., and Updegraff, H.: Sugar Content of Blood and Spinal Fluid in Encephalitis, Arch. Neurol. & Psychiat. **8**:15 (July) 1922.
3. Dopter, C.: Bull. Acad. de méd. **83**:203 (March 2) 1920.
4. Polnovsky, M., and Duhot, E.: Presse méd. **31**:157, 1923.
5. Moates, G. H., and Keegan, J. J.: J. Lab. & Clin. Med. **8**:825-828 (Sept.) 1923.

fluid, reported that the elevation of sugar level, which is known to occur in blood following ether anesthesia, is similarly present in cerebrospinal fluid. They do not, however, suggest any dependency of one sugar level on the other. Recently, Kasahara and Uetani [6] demonstrated a decrease in the reducing power of cerebrospinal fluid following the injection of insulin. They interpret this as proof of the existence of an interrelationship between hyperglycemia and hyperglycorrhachia. The normal sugar value for human cerebrospinal fluid is from 0.04 to 0.068 per cent according to Moates and Keegan [5] and from 0.048 to 0.07 per cent according to Mestrezat.[7] In one case of cerebellar hemorrhage (Case 41 in table) the blood sugar was not estimated but that in the cerebrospinal fluid reached 0.117 per cent. In another case (Case 3, a patient with cerebral tumor) both hyperglycorrhachia and hyperglycemia were reported. Consequently in the table, previous figures in the literature are compiled and no distinction is made between results obtained from blood, cerebrospinal fluid or urine examination.

Cases from the Literature

		Sugar, per Cent			
			Cerebrospinal		
Case	Lesion	Blood	Fluid	Urine	Author and Remarks
1	Tumor cerebri.....	0.237	.....	....	Liefmann and Stern [8]
2	Tumor cerebri.....	0.08	.....	....	Oehlecker [9]; tumor slow growing
3	Tumor cerebri.....	0.158	0.079	....	Thalhimer and Updegraff [2]
4	Tumor cerebri.....	.....	0.042	....	Moates and Keegan [5]
5	Haemorrhagia cerebri.....	0.150	.....	....	Leire [10]
6	Haemorrhagia cerebri.....	0.14	.....	....	Kahler [11]; estimation 3 days after onset
7	Haemorrhagia cerebri.....	0.16	.....	....	Kahler [11]; 10 days after onset
8	Haemorrhagia cerebri.....	0.11	.....	....	Kahler [11]; few days after onset
9	Haemorrhagia cerebri.....	0.12	.....	....	Kahler [11]; 8 days after onset
10	Haemorrhagia cerebri.....	0.10	.....	....	Kahler [11]; 16 days after onset
11	Haemorrhagia cerebri.....	0.13	.....	....	Kahler [11]; 3 days after onset; 10 days after onset 0.10 per cent.
12	Haemorrhagia cerebri.....	0.33	.....	....	Kahler [11]; 2 months after onset; diabetes
13	Haemorrhagia cerebri.....	0.14	.....	....	Kahler [11]; 4 days after onset
14	Haemorrhagia cerebri.....	0.150	.....	....	Feinblatt [12]
15	Haemorrhagia cerebri.....	0.150	.....	....	Feinblatt [12]
16	Haemorrhagia cerebri.....	0.150	.....	....	Feinblatt [12]
17	Haemorrhagia cerebri.....	.....	.....	4.0	Frerichs [13]
18	Haemorrhagia cerebri.....	.....	.....	1.08	Frerichs [13]
19	Haemorrhagia cerebri.....	.....	.....	++	Frerichs [13]
20	Haemorrhagia cerebri.....	.....	.....	0.5	Frerichs [13]; blood in all ventricles
21	Haemorrhagia cerebri.....	.....	.....	0.8	Frerichs [13]; blood in ventricles; pancreas unchanged
22	Haemorrhagia cerebri.....	.....	.....	1.0	Gradwohl [14]
23	Haemorrhagia cerebri.....	.....	.....	3.0	Gradwohl [15]; blood clot in fourth ventricle

6. Kasahara, M., and Uetani, E.: J. Biol. Chem. **59**:433-436 (March) 1924.
7. Mestrezat, W.: Presse méd. **31**:157 (Feb. 17) 1923.
8. Leifmann and Stern: Biochem. Ztschr. **1**:299-308, 1906.
9. Oehlecker: Verhandl. d. deutsch. Gesellsch. f. Chir. 1922, pp. 491-511.
10. Leire, cited by Bang, I.: Der Blutzucker, Wiesbaden, 1913, p. 123.
11. Kahler, H.: Wien. Arch. f. inn. Med. **4**:129-148 (April) 1922.
12. Feinblatt, H. M.: J. Lab. & Clin. Med. **8**:500-505 (May) 1923.
13. Frerichs: Ueber den Diabetes, Berlin, Hirschwald, 1884.
14. Gradwohl: M. Rev. **40**:61-64, 1899.
15. Gradwohl: Philadelphia M. J., 1899, cited from Gradwohl (Footnote 14).

Cases from the Literature—Continued

Case	Lesion	Sugar, per Cent: Blood	Cerebrospinal Fluid	Urine	Author and Remarks
24	Apoplexia	0.308	.....	....	Hollinger [16]
25	Apoplexia	0.219	.....	....	Hollinger [16]
26	Apoplexia	0.123	.....	....	Hollinger [16]
27	Apoplexia	0.09	.....	....	Kahler [11]; 1 year before apoplexia; few days before analysis slight attack
28	Apoplexia	.....	.....	0.69	Frerichs [13]; blood in all ventricles
29	Apoplexia	.....	.....	0.50	Frerichs [13]; polarimetric analysis
30	Apoplexia	.....	.....	0.8	Frerichs [13]; third and fourth ventricles filled with blood
31	Apoplexia	.....	.....	0.69	Frerichs [13]; blood in all ventricles; pancreas unchanged
32	Apoplexia	.....	.....	1.08	Frerichs [13]; liquid blood in all ventricles; pancreas unchanged
33	Apoplexia	.....	.....	2.96	Schuetz [17]; polarimetric estimation; 14 months later another attack with 2.4 per cent. urine sugar; period between the two attacks sugar-free urine
34	Apoplexia	.....	.....	0.22	Loeb [18]
35	Apoplexia	.....	.....	0.4	Loeb [18]
36	Apoplexia	.....	.....	++	Ollivier [19]; sugar appeared 1 hour after onset and disappeared within 7 hours
37	Apoplexia	.....	....	++	Ollivier [19]; sugar appeared 1½ hours after onset and disappeared in about 7 hours
38	Edema cerebri	.....	.....	0.2	Gradwohl [14]; sugar in urine for 3 days; Bremer's blood test positive until fifth day
39	Echinococcus cerebri	0.12	.....	....	Oehlecker [9]
40	Echinococcus basis cerebri	0.12	.....	0	Oehlecker [9]
41	Haemorrhagia cerebelli	.....	0.117	....	Moates and Keegan [5]
42	Haemorrhagia pontis	0.15	.....	....	Kahler [11]; 2 days after onset
43	Haemorrhagia pontis	0.13	.....	....	Kahler [11]; 3 days after onset
44	Haemorrhagia pontis	0.12	.....	....	Kahler [11]; slight attack 14 days before analysis
45	Haemorrhagia pontis et medullae oblongatae	.....	.....	++	Parkes [20]; blood clot encircling the medulla; urine examined postmortem
46	Haemorrhagia pontis et ventriculi quarti	.....	.....	++	Markwordt [21]; urine examined postmortem
47	Tumor medullae oblongatae	.....	.....	++	Reimer [22]; tumor growing into fourth ventricle
48	Tumor tbc medullae oblongatae	.....	.....	6.0	De Jonge [23]
49	Tumor sarcoma medullae oblongatae	.....	.....	6.0	Dompeling [24]
50	Tumor plexus chorioidei ventriculi quarti	.....	.....	++	Levrat-Perroton [25]
51	Tumor plexus chorioidei ventriculi quarti	.....	.....	5.0-8.0	Von Recklinghausen [26]
52	Haemorrhagia ventriculi quarti	.....	.....	2.0	Gradwohl [14]; Bremer's blood test positive
53	Cysticercus ventriculi quarti	.....	.....	++	Alt [27]; patient showed periodic glycosuria
54	Cysticercus ventriculi quarti	.....	.....	2.5	Michael [28]

16. Hollinger, A.: Biochem Ztschr. **17**:1-12, 1909.
17. Schuetz: Prag. med. Wchnschr. **50**:613-615, 1892.
18. Loeb: Prag. med. Wchnschr. **50**:615-616, 1892.
19. Ollivier: Gaz. Hebd. de méd. **11**:164-167, 1875.
20. Parkes: Lancet **2**:149-150, 1860.
21. Markwordt: Arch. f. klin. Med. **18**:111, 1876.
22. Reimer: Jahrb. f. Kinderheilkunde, 1876, pp. 306-308.
23. De Jonge: Arch. f. Psychiat. **13**:658-670, 1882.
24. Dompeling: Nederl. Arch. v. geneesk. **4**:179-190, 1869.
25. Levrat-Perroton: These, Paris, 1859, cited by de Jonge (Footnote 23).
26. Von Recklinghausen: Arch. f. path. Anat. **30**:360-376, 1864.
27. Alt: Neurologisches Zentralblatt, 1902, p. 567.
28. Michael: Deutsch. Arch. f. klin Med. **44**:597-604, 1889.

Only a few cases can be found in the literature in which there was compression limited to the medulla oblongata and in which the sugar content either of blood or of urine was examined. Weber's [29] case of a tumor of the roof of the fourth ventricle of the brain was accompanied by glycosuria (3 per cent), but was complicated by fibrous changes in the pancreas. Osler [30] observed a woman with cysticercus in the fourth ventricle, but this case was complicated by the presence of diabetes mellitus. Michael [28] described another case of cysticercus of the fourth ventricle in which there was 2.5 per cent sugar in the urine. But the most interesting instance of this type is a patient, observed by Alt,[27] who showed a periodical glycosuria in which there may have been a causative connection between the local pressure exerted at certain times by the cyst on the medulla oblongata and this periodicity of the glycosuria. Other cases, shown in the table, in which mechanical compression of the medulla seems to have been probable (Cases 45 to 54) were all accompanied by glycosuria.

Besides these clinical findings on human beings affected with lesions of the central nervous system, there have been certain observations made during experiments on blood sugar in decerebrate animals [31] which seemed to indicate an importance in hyperglycemia of mechanical stimulation of the persistent part of the central nervous system. Some decerebrated animals showed marked symptoms of medullary stimulation, especially slow and deep breathing; necropsy of these animals usually showed a blood clot lying on the ventral surface of the medulla oblongata. Frequent analyses of their blood gave sugar figures not only far above normal average values but also above figures obtained from animals similarly operated on but without hemorrhage.

On the basis of the foregoing collected findings the present work has attempted to decide:

1. Whether mechanical compression of the medulla oblongata, acting without injury to its nervous tissue, causes carbohydrate mobilization.

2. Whether an increase of cerebrospinal fluid pressure acting on the whole central nervous system gives the same result, i. e., a hyperglycemia.

METHODS USED AND CONTROL OBSERVATIONS

Two chief series of experiments were devised to meet these problems. To create mechanical compression of the medulla, small amounts of paraffin or blood were injected into the cisterna magna; in both

29. Weber: Internat. Clinics **4**:78-87, 1921.

30. Osler, cited by H. Feinblatt (Footnote 12).

31. Bazett, H. C.: Tychowski and Crowell: Proc. Soc. Exper. Biol. & Med. **22**:39-42, 1924.

cases the substance introduced acted simply as a foreign body. An increase of cerebrospinal fluid pressure was obtained by continuous injections of fluid into the cavum subarachnoidale. Sugar variations were followed by frequent blood analyses.

Animals Used and Their Treatment During Experiments.—Cats were used in all experiments. To avoid active digestion and emotional processes the animal was isolated and made to fast from sixteen to twenty-four hours before the beginning of the experiment. No previous special diet was provided.

The anesthetized animal was placed on a specially heated table and its position was not disturbed throughout the experiment. By the intermittent use of the heating apparatus an approximately constant rectal temperature was maintained; otherwise the temperature tended to fall during the first two or three hours.

Anesthesia.—The effect on blood sugar of a great number of anesthetics is well established. Particularly chloroform and ether elevate the sugar to so high a level that any changes at this level are difficult to interpret. It was therefore necessary to use only such anesthetics as do not of themselves cause hyperglycemia; further, these had to assure prolonged and uniform anesthesia when given in sufficient amount at the beginning of an experiment. Hypnotics rather than anesthetics give such results.

Three drugs were used: (1) chlorbutanol (trichlor-tertiary-butyl alcohol); (2) iso-amyl-ethyl barbituric acid; (3) barbital sodium (sodium diethyl-barbituric acid), and (4) chloroform, for a few control experiments.

The first drug used was chlorbutanol. This, because of its insolubility in water, was kept in 12.5 per cent alcoholic solution. Measured amounts of this standard solution were diluted to 25 cc. with warm water and administered through a stomach tube. The dosage was 0.17 Gm. per kilogram of body weight. Thus, about 1 cc. of alcohol per kilogram of body weight was given along with the anesthetic. Such an amount would not increase the blood's reducing power; rather would it diminish it, as shown by Blatherwick, Maxwell and Long [32] in their experiments on rabbits; Fuller's [33] work on diabetic patients confirms in human beings these experimental findings. Some animals, probably as a result of the alcohol, became restless and excited before attaining complete anesthesia. This was reached in from about ten to twenty minutes. Corneal reflexes remained.

32. Blatherwick, N. R.; Maxwell, and Long, M. L.: Am. J. Physiol. **67**:346-347, 1923.

33. Fuller, L. S.: J. Metabolic Res. **1**:609-617 (May) 1922.

The second drug, iso-amyl-barbituric acid, has been investigated by Page,[34] who found it a satisfactory anesthetic and one with little or no influence on blood sugar. We used it in a few experiments in his doses (from 0.09 to 0.12 Gm. per kilogram) with results that confirmed his work. Because of its insolubility the drug was first converted into sodium salt by tenth normal sodium hydroxid solution, after which it was given by stomach tube in 25 cc. of water.

We used most often the last preparation, barbital sodium, a barbituric acid derivative recently investigated by Dox [35] and Ellis.[36]. It is easily soluble in water and is of prolonged and uniform effect; from 0.25 to 0.35 Gm. per kilogram of body weight, dissolved in 25 cc. of water and given to a fasting animal by stomach tube, will produce a complete surgical anesthesia in from twenty to forty-five minutes which may last for days. Control experiments were made to test the effect of barbital

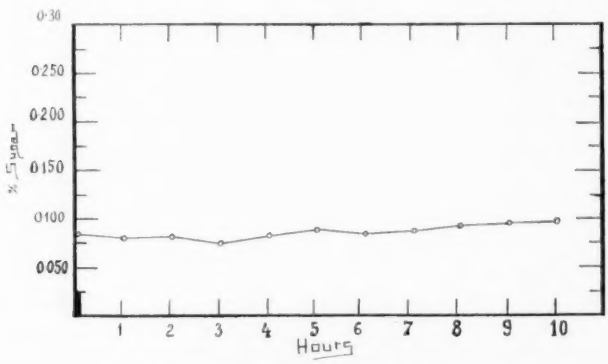

Fig. 1.—Effect of barbital sodium on blood sugar.

sodium on blood sugar and gave negative results, except for an occasional slight decrease during the first two or three hours. Figure 1 shows such a control experiment.

A peculiar effect of the drug, noted in almost every experiment, was an irritation of the nasal mucous membranes, manifested by sneezing; there also was a dilatation of the small blood vessels of the ears and mucous membranes of the nose and mouth. Blood pressure records showed diverging systolic and diastolic levels though mean pressure was unchanged. The vessel dilatation usually disappeared after three or four hours.

A few experiments were performed under chloroform. We hoped that they would show that the same factors were effective even at high

34. Page, I. H.: J. Lab. & Clin. Med. **9**:3, 1923.
35. Dox: J. Am. Pharm. A. **12**:602-609, 1923.
36. Ellis: J. Parm. & Exper. Therap. **21**:323-342 (June) 1923.

sugar levels but the results were somewhat complicated. The chloroform was given through a trachea cannula. All connections were as short as possible; a screw clip altered the amount of admixed air and was adjusted so as to maintain a light anesthesia.

"Normal" Blood Sugar in Cats.—There is no steady sugar level in blood; it changes continuously. Exertion affects it; so does body temperature, emotional disturbances and food intake; and in a larger sense the animal's nutrition is important because of its influence on available glycogen. These changes can all be kept within certain physiologic limits, however, if the proper anesthetic is used and the experiments standardized.[37]

The literature on normal blood sugar in cats is conflicting. Scott [38] stated the normal average blood sugar in cats to be 0.069 per cent. Abderhalden [39] found in one analysis 0.0851 per cent. Pavy [40] obtained an average of 0.088 per cent from six estimations (cardiac blood). Boehm and Hoffmann [41] from twenty-six estimations, including three animals fasted eight days, gave 0.15 per cent, with the limits of 0.11-0.31 per cent. Mellanby [42] considers the normal content to be about 0.2 per cent and Rona and Takahashi,[43] using polarimetric methods on four animals, reported variations between 0.154 and 0.355 per cent, with an average of 0.28 per cent. Griffith [44] doubts the existence of a "normal" blood sugar value, pointing out individual variations, changes arising from simple handling of the animal before anesthetization, from anesthetics or from operations in the course of the experiments.

In spite of the foregoing divergent findings there must exist limits that the normal animal does not exceed. Many of the foregoing figures are often evidently too high; with a blood sugar of 0.3 per cent or even much lower, glycosuria appears; such values must therefore be considered as a hyperglycemia.

A number of standardized experiments were performed, without anesthesia, to define those limits for cats. The animals received their last meal twenty-four hours before the estimation and were isolated in a quiet room. Blood was taken from the ear by a quick cut with a sharp razor blade, while the assistant stroked the cat. No pain reaction was noted. The following figures were obtained: experiment 1, 0.076 per cent; experiment 2, 0.0625 per cent; experiment 3, 0.055 per cent, and experiment 4, 0.066 per cent.

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37. Scott: Am. J. Physiol. **45**:578, 1918.
38. Scott: Am. J. Physiol. **34**:271, 1914.
39. Abderhalden: Ztschr. f. physiol. Chem. **25**:65-115, 1898.
40. Pavy: J. Physiol. **24**:479-517, 1899.
41. Boehm and Hoffmann: Arch. f. Exper. Path. u. Pharmacol. **8**:271-308, 1878.
42. Mellanby: J. Physiol. **53**:1 (Sept.) 1919.
43. Rona and Takahashi: Biochem. Ztschr. **30**:99-106, 1911.
44. Griffith: Am. J. Physiol. **64**:618, 1923.

In one case different treatment was used. The animal was operated on aseptically; the carotid was exposed and ligated and the skin resutured under the exposed vessel; thus about 1.5 cm. of the vessel remained outside. The operation, performed under chloroform, took only a few minutes. Twenty-four hours later blood taken from the exposed vessel showed a sugar content of 0.09 per cent. The first few cubic centimeters of blood were discarded so that only circulating blood was analyzed. No food had been taken since the operation. The rectal temperature at the time of sampling was 38.6 C.

The foregoing figures show that the basal blood sugar of fasting cats approaches the lower limit of the values given in the literature and varies between 0.055 and 0.09 per cent. These limits were used only as a rough basis. In this work one and usually two analyses were always made at the beginning of each experiment and sugar changes occurring during the experiment were compared with this initial level. Any animals with excessively high initial values (such as were often noted to accompany pathologic skin changes) were excluded from further work.

Method and Details of Sugar Estimation in Blood.—Many investigators have shown that an acute anemia is always followed by hyperglycemia. Since in most of the experiments sugar estimations were made every half-hour and since many experiments took ten hours or more, it was necessary to choose a method requiring as little blood as possible, yet sufficiently exact. McLean's [45] method meets both demands, having the additional advantage of being titrimetric. The four hundredth normal sodium thiosulphate solution for this was freshly prepared at the beginning of every experiment and standardized against a known copper solution, which in turn had been checked against a known glucose solution. The errors of the method as tested with a standard glucose solution did not exceed 2 units in the third decimal place ($\pm$ 0.002).

Blood from a clean cut incision of the animal's ear was collected on a paraffined watchglass and 0.2 cc. was taken at once into a micropipet and emptied into the sodium sulphate solution. Quick manipulation rendered any anticoagulant unnecessary. After deproteinization the analysis was in every case completed at once, thus avoiding the addition of antiseptics and excluding glycolysis.

RESULTS OBTAINED

1. *Mechanical Pressure on Medulla Oblongata.*—(*a*) Injections of Paraffin into Cisterna Magna: In attempting to localize mechanical pressure to the medulla oblongata, injections, both of paraffin and

45. McLean: Biochem. J. **13**:135, 1919.

blood, were made through the occipito-atlantal space. In the first case a mixture of solid paraffin and paraffin oil was used, prepared in such proportion that the melting point lay between 34 and 37 C. Measured amounts of the mixture were injected at the temperature of 37 C.

Figure 2 shows the effect on blood sugar of such an injection.

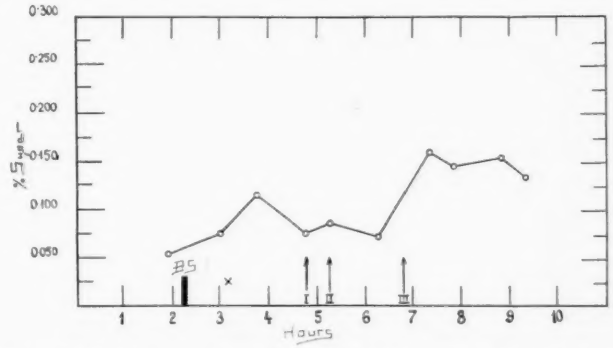

Fig. 2.—Effect on female cat, weighing 2,300 Gm., of barbital sodium anesthesia, *BS;* at *X* puncture of cisterna magna; three injections of 1 cc., 2 cc. and 3 cc. of paraffin are indicated by arrows.

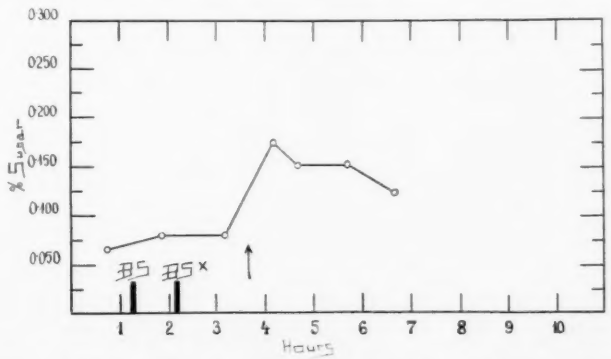

Fig. 3.—Effect on female cat, weighing 2,900 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; sixty minutes later injection of 1.5 cc. of blood into cisterna magna; no change in respiration.

The first two injections produced no marked change in blood sugar; thirty minutes after the third injection the sugar content rose from 0.072 to 0.159 per cent. The last injection also caused a remarkable change in respiration, which even stopped for a few seconds, but soon returned to normal. The animal was killed with ether and its neck cooled by the external application of ether, care being taken not to dis-

turb the animal's position. Necropsy then showed a paraffin clot covering the medulla oblongata with a slight amount going into the cavum cranii.

(*b*) Injections of Blood into the Cisterna Magna: The following experiments were devised to produce the conditions of an "artificial hemorrhage." About 2 cc. of blood were taken from the ear of the cat

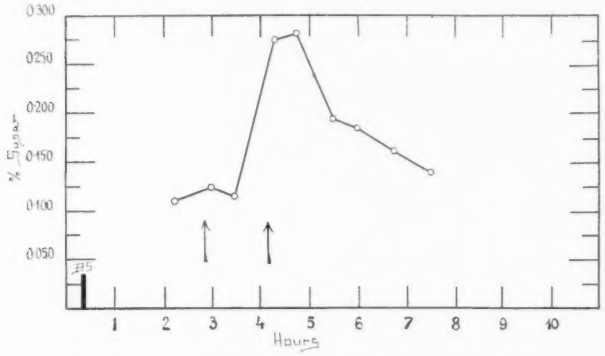

Fig. 4.—Effect on female cat, weighing 3,200 Gm., of barbital sodium anesthesia; at arrows injections of blood: first injection 0.5 cc. into muscles of neck; second, 1.9 cc. into cisterna magna; after second injection respiration became slower and deeper, but soon returned to normal.

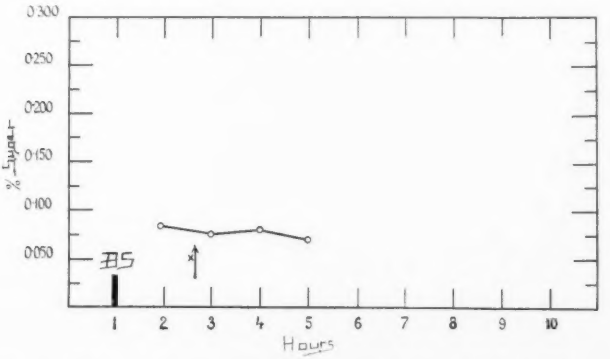

Fig. 5.—Effect on male cat, weighing 2,700 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna, followed by slow (about one minute) injection of 0.5 cc. of blood; no change in respiration; necropsy showed thin and elongated blood clot lying on lower left side of medulla oblongata.

under experimentation. Measured amounts were injected. Animals injected slowly showed no respiratory changes; those injected quickly behaved as in similar experiments with paraffin. Figures 3 and 4 show the results of blood injections.

In the experiment of which the data are given in Figure 3 the sugar content before and after puncture was 0.079 per cent, as against 0.174 per cent eighteen minutes after injection; in that of Figure 4 the first injection of 0.5 cc. of blood was made into the muscles of the neck with a resultant rise of sugar from 0.109 to 0.124 per cent; the second injection into the cisterna magna was followed by a rise from 0.115 to 0.275 per cent. Since it is to be expected that the pressure exerted on the medulla oblongata will depend not only on the amount of blood injected but also on the rate of injection, several experiments were made, in which only comparatively small amounts of blood (from 0.5 to 1.1 cc.) were injected slowly. Two experiments of this type are shown in Figures 5 and 6.

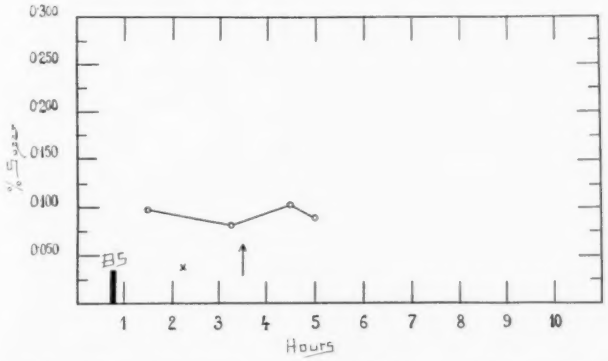

Fig. 6.—Effect on male cat, weighing 3,000 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; at arrow injection of 1.1 cc. of blood into cisterna magna.

Both the foregoing experiments were negative for the blood sugar was practically unchanged. This probably indicates that the mechanical agent is the only effective one, for other conditions in these experiments were the same as in the previous ones.

2. *Hydrostatic Pressure on the Whole Central Nervous System.*—The next part of the work deals with the effect of artificially raising cerebrospinal fluid pressure over longer periods of time; this simulates certain pathologic conditions that are usually associated with hyperglycemia, hyperglycorrhachia and glycosuria, but in which there is no local mechanical pressure on the medulla oblongata Cerebral tumors and hemorrhages distant from the medulla, meningitis, etc., cause commonly a rise of intracranial pressure which is transmitted throughout the craniospinal cavity by the incompressible cerebrospinal fluid.

Although Weed and Hughson [46] state that the cranium and the spinal column with their ligaments in an adult individual constitute, within physiologic limits, an inelastic, rigid container, this closed cavity does not represent a reservoir in which the pressure may be raised artificially and kept on a high level by means of a single injection of a certain amount of fluid. Rocdinski and one of us [47] showed in experiments on dogs and in clinical work on human subjects that such an

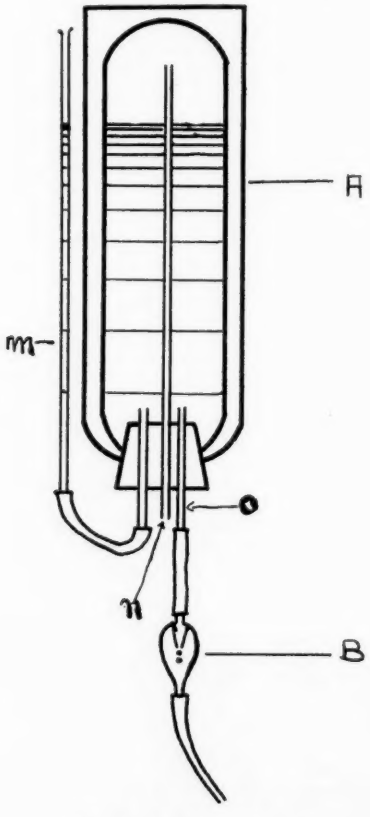

Fig. 7.—Saline reservoir.

artificial rise of cerebrospinal fluid pressure, produced by a single injection of fluid into the subarachnoid space, lasts for a short time only; resorption is rapid enough to restore the initial pressure in a few minutes. To meet this difficulty in the present work a continuous injection

46. Weed, L. H., and Hughson, W.: Am. J. Physiol. **58**:85-100 (Nov.) 1921.
47. Rocdinski and Tychowski: Polska Gazeta Lekarska, 1923, pp. 4-5.

of fluid into the cavum spinale was maintained. For this purpose a needle was inserted into the subarachnoid space either through the membrana atlanto-occipitalis or into the lumbar region. This needle was then connected with an injection apparatus (Fig. 7), constructed of a thermos bottle (*A*) closed with a rubber stopper, provided with three glass tubes: the side glass tube (*m*) showed the fluid level inside of the bottle; *n* allowed air to enter and *O* was for outflow; a drop counter (*B*) indicated the rate of the outflow.

Two solutions were used for injections: isotonic 0.9 per cent sodium chlorid and Ringer's solution [48] without glucose. The fluid was injected at or near the body temperature of the animal, the temperature being measured by a thermometer enclosed in rubber tubing close to the injection needle.

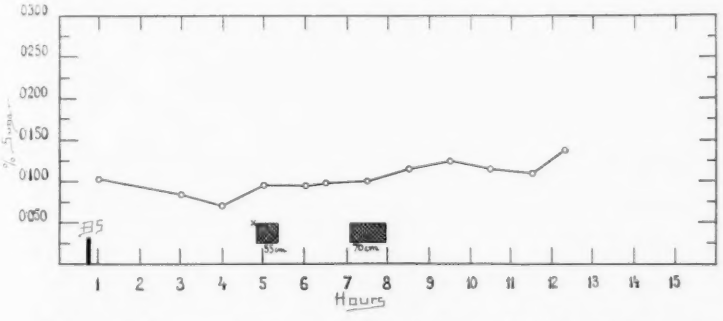

Fig. 8.—Effect on male cat, weighing 3,400 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; pressure exerted: 55 cm. of physiologic sodium chlorid solution for thirty-four minutes and 70 cm. for fifty-two minutes.

Pressure changes were effected by raising or lowering the entire apparatus. The absolute values, expressed in centimeters of the solution used, were estimated between the needle and the fluid surface level in the tube (*m*).

(*a*) Continuous Injections of Saline into the Cavum Subarachnoidale from the Cisterna Cerebellomedullaris After Its Puncture: Figures 8 and 9 show experiments performed according to the technic described in the foregoing; the rise of cerebrospinal fluid pressure thus effected also causes an elevation of the sugar level in the blood.

A rise of pressure to 55 cm. has no marked effect; values from around 80 to 100 cm. are apparently effective. In the experiment of which data are given in Figure 8, 55 cm. of pressure for thirty-four minutes was followed by a rise in sugar from 0.071 per cent to 0.090 per cent, and 70 cm. pressure during fifty-two minutes changed the

48. Bayliss: Prinicples of General Physiology, 1920, p. 211.

blood sugar from 0.098 to 0.124 per cent; but in the experiment shown in Figure 9, 98 cm. of pressure applied for forty minutes produced the change of 0.086-0.128 per cent, and 109 cm. during seventy-five minutes, 0.100-0.140 per cent. It should be noticed that the pressure was raised twice in every experiment, each time causing the same positive result.

An analogous series of experiments was performed, using Ringer's fluid. The experiment shown in Figure 10 corresponds to that shown in

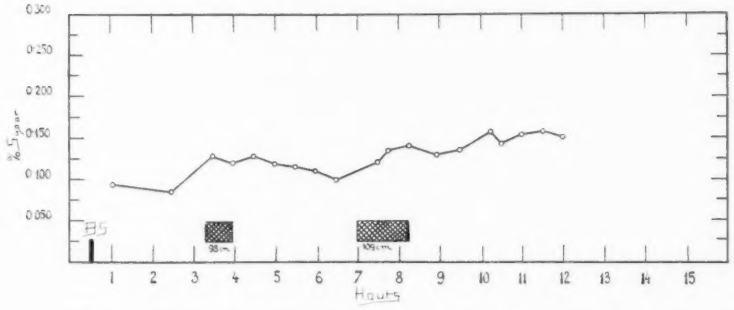

Fig. 9.—Effect on male cat, weighing 2,700 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; pressure: 98 cm. for forty minutes and 109 cm. for seventy-five minutes.

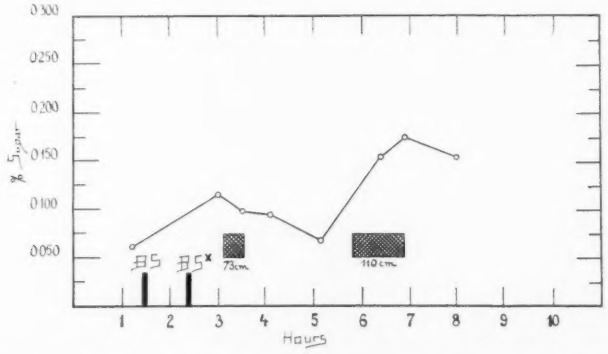

Fig. 10.—Effect on female cat, weighing 2,600 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; pressure: 73 cm. for twenty-three minutes and 110 cm. for sixty-five minutes.

Figure 8: a pressure of 73 cm. for twenty-three minutes was without effect, while 110 cm. applied for sixty-five minutes caused a change in sugar level from 0.068 to 0.175 per cent.

In the experiments of Figures 11 and 12, a pressure of 100 cm. of fluid was applied, each time over a period of sixty minutes.

The blood sugar level rose in one experiment (Fig. 11) from 0.097 to 0.197 per cent and from 0.131 to 0.181 per cent, and in the other (Fig. 12) from 0.115 to 0.178 per cent, and from 0.140 to 0.187 cent. In the latter experiment puncture of the cisterna magna preceded the raising of the pressure by two hours and forty-five minutes. High pressures, such as were used in the following case (Fig. 13), namely 139 cm. for sixty minutes, produced a rise from 0.080 to 0.300 per cent; the second period of pressure, 125 cm. for forty minutes was without effect.

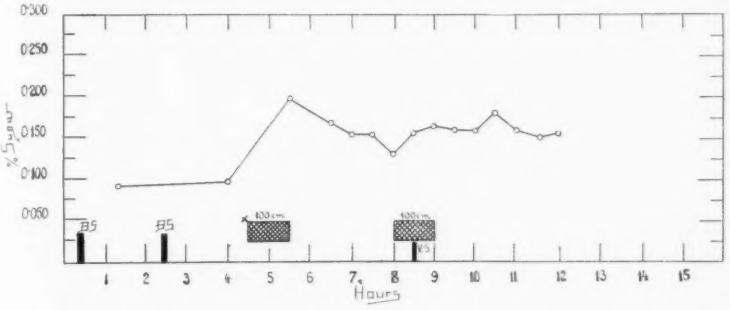

Fig. 11.—Effect on male cat, weighing 4,080 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; pressure: 100 cm. for sixty minutes each time.

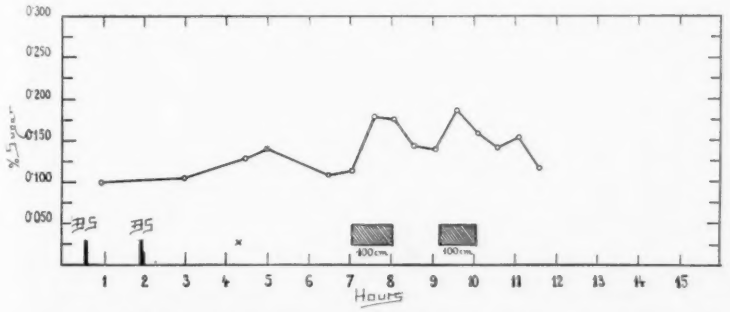

Fig. 12.—Effect on male cat, weighing 2,900 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; pressure: 100 cm. of Ringer's solution for sixty and fifty-five minutes.

In a few cases the pressure in the subarachnoid space was actually measured by a manometer. Two needles were inserted through the atlanto-occiptal ligament into the cerebellomedullar space; one was connected with the pressure apparatus, the other with a manometer. The manometer indicated the pressure in the cisterna and was found to follow closely the applied pressures. The experiment shown in Figure

14 was performed in this manner; fifty minutes of a 50 cm. pressure, as shown by the manometer, did not cause any change in blood sugar. In another experiment 90 cm. of pressure for sixty minutes (Fig. 15) raised the sugar from 0.091 to 0.118 per cent.

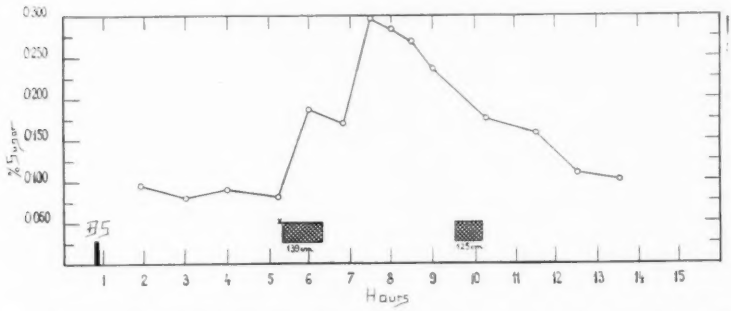

Fig. 13.—Effect on male cat, weighing 3,200 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; pressure: 139 cm. of Ringer's solution for sixty minutes and 125 cm. for forty minutes.

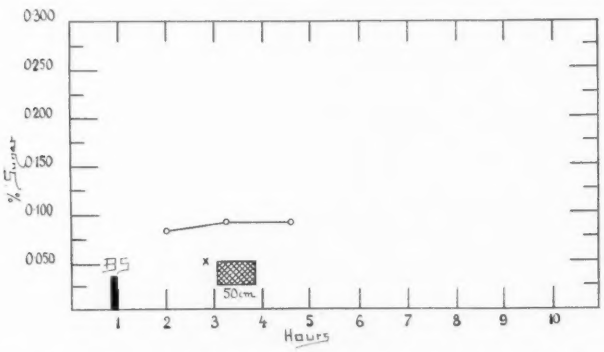

Fig. 14.—Effect on female cat, weighing 2,800 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna; two needles inserted, one connected with a manometer, the other with the pressure apparatus, both filled with Ringer's solution; pressure: 50 cm. controlled by manometer for fifty minutes; no change in blood sugar.

(*b*) Continuous Injections into the Cavum Subarachnoidale from the Lumbar Region: To exclude any possible direct stimulation of the medulla oblongata from the operation, the pressure of cerebrospinal fluid was raised in some experiments by lumbar injection. An ordinary lumbar puncture was performed with a fairly large trochar; the outflow of fluid was taken as proof of a successful puncture. Pressures of different values were then applied.

Figure 16 represents such an experiment in which a positive but slight result was obtained in this way: Eighty-eight centimeters pressure for thirty minutes produced an insignificant rise from 0.077 to 0.090 per cent; 100 cm. for sixty minutes changed the sugar from only 0.080 to 0.098 per cent. In another experiment (Fig. 17), 78 cm. of pressure for sixty minutes raised the sugar from 0.071 to 0.140 per cent, and 80 cm. for sixty minutes from 0.089 to 0.155 per cent.

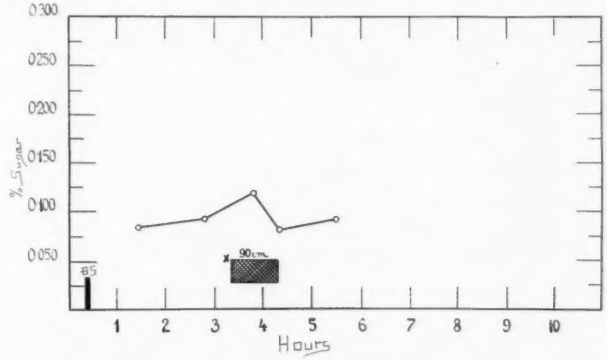

Fig. 15.—Effect on male cat, weighing 4,000 Gm., of barbital sodium anesthesia; at *X* puncture of cisterna magna, two needles inserted, one for pressure apparatus, the other for manometer control; pressure: 90 cm. for more than sixty minutes.

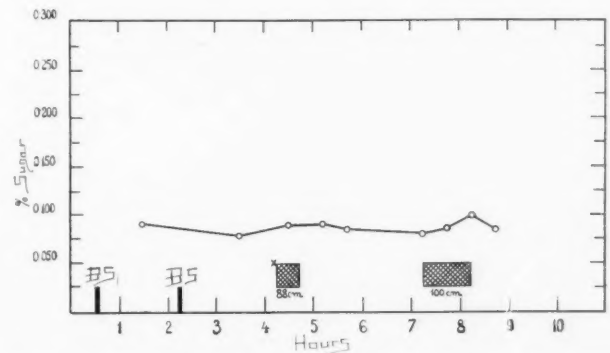

Fig. 16.—Effect on male cat, weighing 2,700 Gm., of barbital sodium anesthesia; at *X* lumbar puncture; pressures: 88 cm. of Ringer's solution for thirty minutes and 100 cm. for sixty minutes.

In a single case (Fig. 18), both methods of raising pressure were used. At first a lumbar injection of physiologic sodium chlorid solution at 100 cm. pressure maintained for sixty minutes raised the blood sugar from 0.087 to 0.114 per cent; two and a half hours later, after the

sugar level had dropped to 0.078 per cent, the cisterna magna was punctured and pressure was then twice raised to 110 cm. for sixty minutes; this resulted in a change of sugar level from 0.078 to 0.131 per cent the first time, and from 0.103 to 0.119 per cent the second.

A number of experiments (seven) were performed on animals under chloroform anesthesia for the reason given at the beginning of the paper.

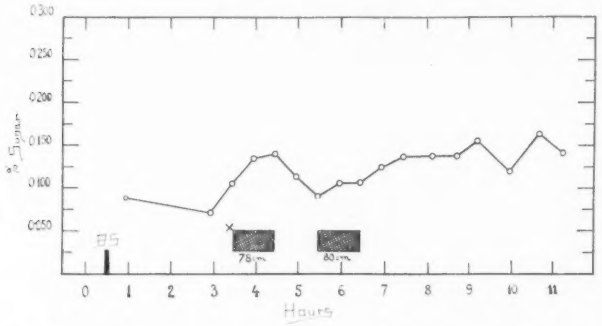

Fig. 17.—Effect on female cat, weighing 3,175 Gm., of barbital sodium anesthesia; at *X* lumbar puncture; pressure: 78 cm. of Ringer's solution in first period and 80 cm. in second, each for sixty minutes.

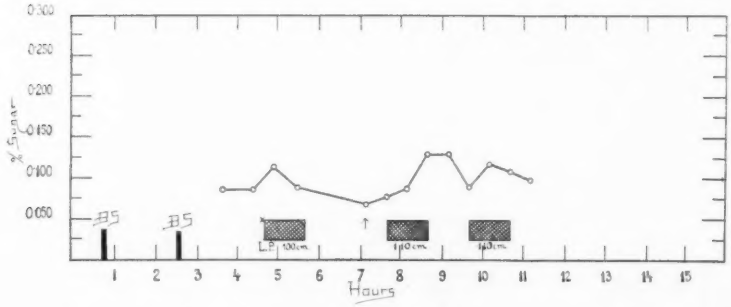

Fig. 18.—Effect on female cat, weighing 2,300 Gm., of barbital sodium anesthesia; at *X* lumbar puncture followed by pressure of 100 cm.; at arrow puncture of cisterna magna, followed by pressure of 110 cm. applied twice, each time for sixty minutes.

Although chloroform itself elevates blood sugar considerably, increased cerebrospinal fluid pressure tended to raise it still more. Figure 19 shows the initial value of blood sugar, 0.193 per cent, one hour after tracheotomy; 93 cm. pressure for sixty minutes brought the sugar to 0.234 per cent.

A slight fall in sugar percentage followed removal of the pressure; two hours later the sugar rose very high as a result of the prolonged anesthesia. In experiment of Figure 20, the rise of cerebrospinal fluid pressure was caused by an injection of 20 cc. of Ringer's solution from a syringe. This sudden change in pressure was followed by an immediate rise of blood sugar from 0.209 to 0.289 per cent.

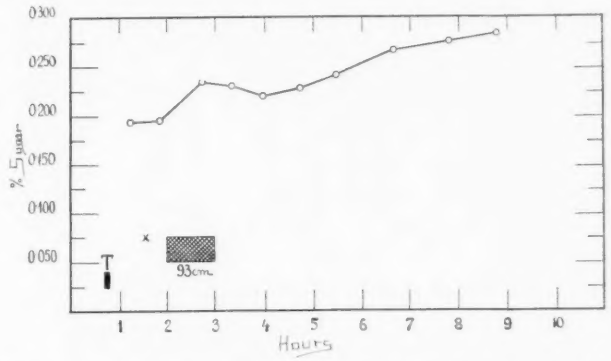

Fig. 19.—Effect on male cat, weighing 2,800 Gm., of tracheotomy at *T*, under chloroform anesthesia; chloroform continued till end of experiment; at *X* lumbar puncture followed by pressure of 93 cm. for sixty minutes.

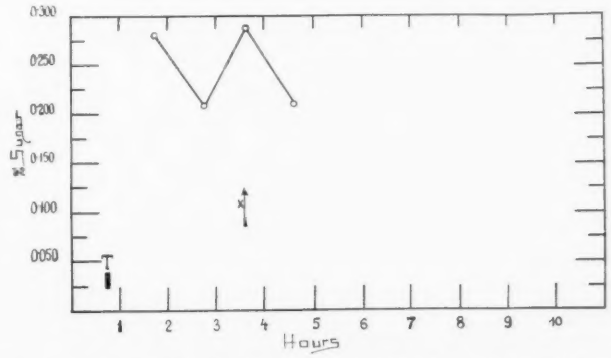

Fig. 20.—Effect on female cat, weighing 3,200 Gm., of chloroform anesthesia; at *T* tracheotomia; at *X* lumbar puncture; at arrow injection of 20 cc. of Ringer's solution from a syringe into subarachnoid space.

3. *Effect of Mechanical Pressure on the Medulla Oblongata and of High Cerebrospinal Fluid Tension on Blood Pressure and Respiration.*—In about 80 per cent of all experiments a more or less marked change in respiration was observed. A considerable change occurred imme-

diately after injections of blood or paraffin into the cerebellomedullar space; it consisted in a decrease in rate and alteration in the depth of respiratory movements. As a result of continuous fluid injections only after a certain degree of pressure was reached, and then only in the first few minutes after starting the inflow did such changes occur and they were less pronounced. Apparently the pressure affected the respiratory centers of the medulla. The possibility arose that other medullary centers might be altered at the same time, especially the sensitive vasomotor centers and vagus nuclei, both of which are closely connected with the maintenance of blood pressure. Since it is well known that both respiratory disturbances and changes in blood pressure greatly affect blood sugar, it seemed advisable to determine how these altered as a result of the application of our experimental methods. Finkelnburg [49] stated from his experiments on dogs, in which he investigated the transmission of cerebrospinal fluid pressure throughout the craniospinal cavity, that pressure raised in the lumbar region is not exerted to the same degree within the cranium, and that an even more marked difference of levels may be observed when the intracranial pressure is primarily raised. He also noted marked slowing of pulse rate and respiratory movements as the result of pressure from around 80 to 100 mm. of mercury; his method of pressure raising was identical with that of continuous saline injection used in the present work; a gradual increase of the pressure followed by its prolonged application did not usually affect the circulatory and respiratory mechanisms.

We performed a series of experiments in which the respiratory movements were recorded by a modification of Cushny's method;[50] blood pressure was taken with Hürthle's manometer, and the changes in cerebrospinal fluid pressure were also recorded with a sensitive manometer of Hürthle's type connected with the punctured cisterna magna; pressure was applied either by blood injection or by the saline injection apparatus in the usual way.

The injection of 2 cc. (Fig. 21) of blood into the cisterna magna produced a slight but definite rise in the cerebrospinal pressure which was partly maintained above the previous level; the blood pressure showed a rise of only about 10 per cent, but returned to its previous value within about two minutes; the respiration was irregular, showing long inspiratory pauses, but it also returned to normal within about one and a half minutes. With a larger injection of about 4 cc. of blood into the same animal about five minutes after the first, a much greater rise of cerebrospinal pressure occurred (an additional increase of 50 per cent) followed by a gradual drop, though even after many minutes the pressure still

49. Finkelnburg: Deutsch. Arch. f. klin. Med. **76**:383-412.
50. Cushny: J. Pharm. & Exper. Therap. **4**:363, 1913.

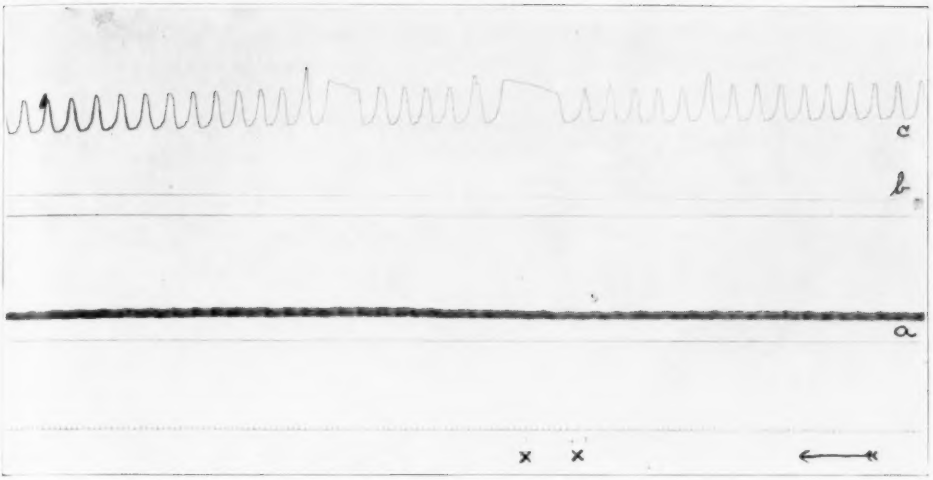

Fig. 21.—Effect on female cat, weighing 3,000 Gm., of barbital sodium anesthesia; *x-x*, injection of 22 cc. of blood into cisterna magna, followed by slight rise in cerebrospinal fluid pressure; *a*, blood pressure; *b*, cerebrospinal fluid pressure; *c*, respiration, upstroke—inspiration; after about twenty seconds an insignificant rise in blood pressure (carotid) accompanied by increased pulse pressure; stoppage of respiratory movements immediately after injection was started; record reads from right to left; time marker indicates seconds.

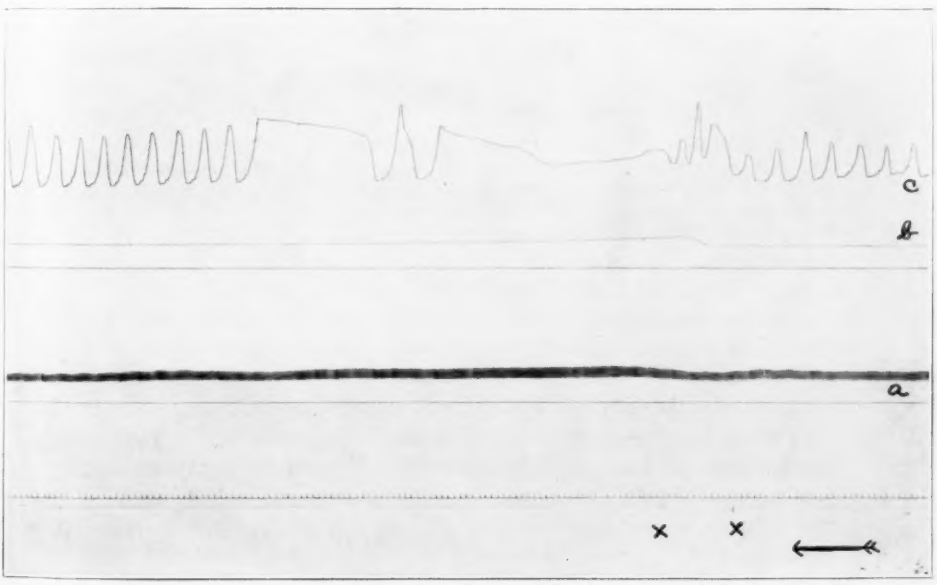

Fig. 22.—Effect of injection of additional blood into same animal as in Figure 21 (description in text).

remained about 25 per cent above the level at the beginning of the experiment. The blood pressure changes were still slight (about 20 per cent) and the previous level was regained within three minutes; the respiratory changes were much more marked, long inspiratory spasms occurring (Fig. 22 indicates type of result obtained).

When saline is injected into the cisterna magna continuously and slowly so that the pressure rises much more gradually the effect on the respiration is much less, there being a marked slowing of the respiratory movements. Figure 23 indicates the blood pressure and respiratory changes seen as the result of raising the pressure in the cisterna magna to 100 cm. of saline pressure. Similar results were obtained to those reported by Finkelnburg,[49] Naunyn and Schreiber,[51] but were obtained with much lower pressures.

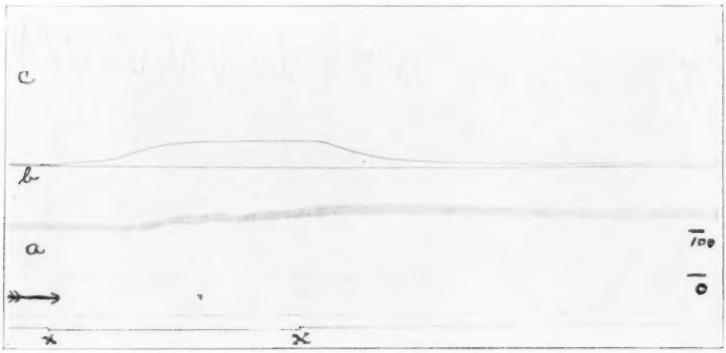

Fig. 23.—Effect on female cat, weighing 2,800 Gm., of barbital sodium anesthesia; blood pressure taken from the carotid, respiration recorded by the spirometer; two needles inserted in cisterna magna, one connected with Hürthle's manometer, the other with the pressure apparatus; *x-x*, raising of cerebrospinal fluid pressure to 100 cm. of Ringer's solution.

COMMENT

In these experiments every effort was made to eliminate factors that might complicate results. Temperature, active digestion, the so-called "Fesselungshyperglykaemie" and anesthesia, any or all may have come into play; their possible influence is to be considered.

Temperature was controlled by frequent observations of a rectal thermometer. The slight fall attending the early hours of the anesthesia was prevented by the use of a heating arrangement and body temperature did not vary over a few tenths of a degree Centigrade. Even greater variations than this occur physiologically and apparently do not affect

51. Naunyn and Schreiber: Arch. f. exper. Path. u. Pharmakol. **14**:1-112, 1881.

blood sugar. The intake of carbohydrates from the alimentary canal was nil, the animals being starved for at least sixteen hours before the first blood sample was taken. "Fesselungshyperglykaemie" was avoided by the use of anesthetics; the animals lay unconfined on the operating table.

The influence of anesthetics has already been described. In seven experiments performed under chloroform there was a high sugar level, which after several hours of a fairly steady level rose even higher. This may well correspond to the exhaustion of chromophil material in prolonged narcosis observed by Schur and Wiesel [52] and confirmed by Borberg. McGuigan and Ross [53] noted an increase of blood sugar even in moribund animals immediately before death, observations which may explain cases in the present work in which the sugar went up at the end of the experiment apparently without reason. The total period of observation of the chloroform narcoses was considerably shorter than the others, never more than five hours, because of secondary changes from the prolonged anesthesia, i. e., exhaustion of available glycogen, toxic effect of chloroform on heart muscle and liver tissue, and dehydration of the animal, consequent on breathing through the tracheotomial cannula. Under these limitations the most favorable time for actual experimentation was the first two or three hours after the beginning of anesthesia, when these factors were not yet potent enough to obscure results, but late enough to avoid the effect of tracheotomy. The experiments under chloroform showed in general similar results to those under other anesthetics. Even such high sugar levels as from 0.15 to 0.21 per cent were elevated by the use of pressure on the medulla oblongata.

In the first series of experiments, in which the subarachnoid space near the medulla oblongata was entered, the possibility of injury to the bulb or cervical cord, or even of a regular piqûre, all of which might result in hyperglycemia, was a pertinent danger. To avoid these the needles were introduced very slowly and directed upward to one side. After the experiment a necropsy was always performed and the spinal cord and bulb macroscopically examined for injury. The second series of experiments excluded this danger because pressure was applied from the lumbar region; results were just as positive.

To maintain a constant hydrostatic pressure continuous injections were made; the fluid, physiologic sodium chlorid solution or Ringer's solution was allowed to flow in for from twenty-three to seventy-five minutes. Besides pressure changes two other possible effects of such

52. Schur and Wiesel: Wien. klin. Wchnschr., 1908.
53. McGuigan and Ross: J. Biol. Chem. **22**:418, 1915.

prolonged injections are to be considered, first, the dilution of the cerebrospinal fluid, with its resultant chemical effect on the central nervous system; second, the resorption of a considerable amount of the injected fluid into the blood and lymph, with a consequent change in blood volume. As to the first, neither fluid showed any influence on blood sugar, even when used over long periods; this is shown when the flow of fluid into the subarachnoid space was continued for hours under low pressure without change of blood sugar. The possible chemical effect on the nervous system of the potassium and calcium salts in the fluids used is to be especially considered, since Hooker [54] and Mathison [55] demonstrated their stimulative powers on medullary and spinal centers. However, not only because of the low concentration but also because of the antagonistic action of calcium to potassium ions, both of which are present in Ringer's solution, any effect is absent, as proved by Heinekamp.[56] Even should toxic effects appear, the changes in the tissues must remain and recovery would be impossible within the time of the experiment. Actually, however, repeated raising and lowering of the pressure resulted in increases and decreases, respectively, of the sugar content of the blood. This marked sequence of the blood sugar variations to pressure changes suggests strongly that the mechanical factor alone is responsible for the final effect.

Probably the second possibility, a change in blood volume through resorption, actually does take place, but the effect on blood sugar must be a lowering of its percentage, and any slight degree of hydremia which may have developed from the prolonged injection would tend rather to obscure than to accentuate the simple pressure effects.

The time between sugar estimations varied from fifteen to sixty minutes. Even within such intervals oscillations in blood sugar content may occur. However, it seems that the sugar curve was followed closely enough for the purposes of this work. The stimuli applied were, in the case of continuous injections, of considerable duration and their effects, if any, probably last longer than fifteen minutes, our shortest interval. Moreover, in the course of the work it was found that the changes in blood sugar from such rather weak though prolonged stimuli occur slowly, so that the usual interval of thirty minutes was close enough to follow them accurately.

There remain about 10 per cent of the experiments, in which results were negative. The larger number of these followed stimulation by hydrostatic pressure; only in a few cases was the injection of blood ineffective. As to the first series, it seems that a certain degree of

54. Hooker: Am. J. Physiol. **38**:200-208, 1915.
55. Mathison: J. Physiol. **13**:471-494, 1911.
56. Heinekamp, W. J. R.: J. Pharm. & Exper. Therap. **19**:239-245 (April) 1922.

pressure can be applied with practically no effect on sugar. If values around 100 cm. are reached, changes are marked. It was also noted that the same degree of pressure exerted through a large trochar produced a more marked effect than pressure applied through a small bored needle. Thus, rate of the initial change of pressure seems to be a factor of great importance. Negative results in cases of blood injections may also be easily explained, and in some experiments (Figs. 5 and 6) were expected, for the blood was purposely injected in a small amount, 0.5 cc., and the injection performed very slowly. Thus conditions were not favorable to the development of pressure; the small amount of fluid introduced under low pressure over a comparatively long time was easily taken care of by resorption of a corresponding amount of cerebrospinal fluid, and the insignificant change in pressure during the injection was apparently far below the stimulation threshold.

Moreover, on a starved animal even Bernard's piqûre is ineffective, because of lack of available glycogen. The cats in the present work were without food—for other reasons—for at least sixteen hours before being used, and their previous food was not especially rich in carbohydrates. The resultant low glycogen should then be considered as probably an important factor in cases of negative or only weakly positive results.

Finally, the depressive effect of the anesthetics on the central nervous system must be taken into account. Although the doses used were not excessive and corneal reflexes were usually present, it is to be expected that under physiologic conditions the same stimulation would produce a more marked hyperglycemia.

Explanation of the positive results obtained in this work is closely related to the theories concerning Bernard's piqûre. Though used in experimental work for more than half a century, the piqûre was performed without accuracy or definite location; experimenters limited themselves to macroscopic examination of the involved part of the medulla oblongata, and only recently Brugsch, Dresel and Lewy [57] first used systematic histologic controls, following both positive and negative piqûres. Their work led them to state that the essential agent in the production of piqûre-hyperglycemia is a lesion of the so-called "sympathetic" nucleus nervi vagi, which contains not only sympathetic but also parasympathetic cells. They were able to state further that minute hemorrhage near this center could, without actually destroying the cells, produce a stage of "irritation" characterized by microscopic changes, such as are sometimes produced by partially successful piqûre, and that this also was followed by hyperglycemia. Moreover, they found

57. Brugsch, T.; Dresel, and Lewy: Ztschr. f. exper. Path. u. Therap. **21**: 358-379, 1920; Ztschr. f. d. ges. exper. Med. **25**:262-270, 1921.

that lesions of different parts of this nucleus produced contrary changes in blood sugar; they consider that injury of the caudal part involved the sympathetic cells concerned in activation of the suprarenals, and so represented the common piqûre lesion; the rostral segment, which includes the vagus parasympathetic central elements, they considered to be related to the internal secretion of the pancreas and thought that its stimulation leads to increased polymerization of glucose into glycogen.

Closely related to this sympathetic nucleus nervi vagi is a group of ganglionic cells situated in the hypothalamus, which was discovered by retrograde degeneration and described by Molhant.[58] This nucleus paraventricularis, located close to the third ventricle, is considered by many to be a center superposed in a functional sense to the nucleus sympatheticus nervi vagi; the relation is suggested by certain anatomic changes occurring in both nuclei in cases of paralysis agitans, observed by Lewy. The relation of the nucleus paraventricularis to carbohydrate mobilization is not yet clear; but the anatomic findings of Lewy seem to indicate that the two centers collaborate to increase sympathetic tonus, which is considered by some essential to the development of hyperglycemia.

The mechanical pressure applied to the medulla must affect not only the sympathetic and the paraventricular nuclei but also other medullary centers. The changes in respiration that resulted were at first only observed and noted, but in later experiments they were also recorded. An analysis of the curves obtained shows a decrease in both rate and depth of respiratory movements. The consequent deficient lung ventilation followed by lowered hemoglobin saturation may induce anoxemia, which is known to create a powerful stimulus toward the development of hyperglycemia. Such changes should occur provided the pressure does not stimulate other and more powerful antagonistic centers.

The nucleus motorius nervi vagi is largely concerned with the innervation of not only the abdominal but also the thoracic viscera; most important of these are the heart and the lungs. Blood pressure tracings obtained from the carotid did not indicate any marked cardiac changes; far more complicated are the vagal effects on the lungs. Fibers innervating the bronchial system can greatly influence the individual lumina and these may so alter the air exchange as to bring on anoxemia. Vagus stimulation may also alter the patency of the pulmonary blood vessels through their rich vasomotor supply, a fact demonstrated by Krogh [59] and by Carlson and Luckhardt,[60] and thus in still another way may

58. Molhant: Nevraxe, Louvain, 1910, pp. 137-244.
59. Krogh: Zentralbl. f. Physiol. **20**:802, 1907.
60. Carlson, A. J., and Luckhardt, A. B.: Am. J. Physiol. **56**:7-2112 (May) 1921.

regulate the air exchange. All these factors might be combined at once from medullary stimulation but the final effect would be asphyxia.

Macleod [61] and Griffith [44] demonstrated by experimentation that stimulation of the central end of the vagus produced a rise in blood sugar; Rossi [62] after similar stimulation of the vagus found a diminution of the glycogen content of the liver. These experiments show that the afferent fibers of the vagus are concerned in the metabolism of carbohydrates.

In our experiments whenever blood pressure was recorded it preserved an almost constant level. The slight rise that did occur was preceded by changes in respiration and did not take place immediately after medullary compression but only after a certain latent period. The fact that this rise was slow to appear indicated that it was a response of the vasomotor centers either directly due to the pressure or secondary to the respiratory changes. Winkin [63] showed that the cutting off of the arterial circulation to the head produced a marked vasoconstriction; she further showed that both splanchnic nerves together with their secretory fibers to the suprarenals are pathways for impulses originating in the vasomotor centers and passing down to the peripheral organs. The increased output of epinephrin which is said to follow central stimulation and to maintain the primary vasoconstriction may be responsible for the sugar mobilization. Cannon and Rapport [64] state the existence of a reflex center for epinephrin secretion which they believe to be located on the floor of the fourth ventricle and to be the recipient of both excitatory and inhibitory impulses. In either case, be it alteration of vasomotor centers or stimulation of Cannon's epinephrin center, medullary pressure may result in an increased discharge of epinephrin followed by an increased sympathetic tonus and subsequent hyperglycemia; this fits in well with the theory of hyperglycemia which has been widely accepted since Blum's discovery of the glycosuric effect of epinephrin. The action of epinephrin was thought by Masing [65] to be manifested by a lowered gas exchange in the isolated liver; according to Neubauer [66] it produces an anoxybiotic state in the liver; Starkenstein [67] believes that stimulation of the sympathetic results in a change of the physical constitution of the cells, which represents a uniting link between ferment action and sympathetic nerve endings, consisting in an alteration of osmotic pressure and surface tension. Gottschalk and

61. Macleod: Am. J. Physiol. **19**:388, 1907.
62. Rossi: Arch. di fisiol. **14**:273-277, 1916.
63. Winkin: Proc. Soc. Exper. Biol. & Med. **18**, 1921.
64. Cannon, W. B., and Rapport, D.: Am. J. Physiol. **58**:308 (Dec.) 1921.
65. Masing: Arch. f. exper. Path. u. Pharmakol. **69**:431-457, 1912.
66. Neubauer: Biochem. Ztschr. **43**:335-345, 1912.
67. Starkenstein: Ztschr. f. exper. Path. u. Therap. **10**:78-119, 1911-1912

Pohle [68] make the change of hydrogen ion concentration in the blood of the portal vein and in liver tissue fluid responsible for the glycosuric action of epinephrin.

The survival of the hyperglycemia in some of our experiments beyond the application of medullary pressure may correspond to the observations of Billigheimer,[69] and those also of Heténvi and Lax,[70] in which the epinephrin hyperglycemia far outlasted the changes in blood pressure and pulse rate.

A quite different view of the origin of hyperglycemia from intracranial changes is advanced among others chiefly by Cushing [71] and recently by Brugsch, Dresel and Lewy.[72] By experimentation he seems to have demonstrated some influence of the posterior lobe of the hypophysis cerebri on carbohydrate metabolism; the product of its secretion first enters into solution in the cerebrospinal fluid, then probably by way of the dural sinuses passes into the blood stream. He considers that compression of the aquaeductus sylvii by tumors or lesions of the posterior lobe by trauma may alter the production or transportation of this secretion and in consequence may produce a hyperglycemia.

Another attempt to introduce the endocrine system as a factor in the regulation of carbohydrate metabolism was made by Eppinger, Rudinger and Falta.[73] They proposed an interrelationship between the secretions of the suprarenals, the hypophysis and the thyroid, and supposed that the level of blood sugar was determined by changes in the balance of these glands.

Our own results do not give any evidence as to the mode of origin of the hyperglycemia, except that it seems improbable that it results simply from asphyxia secondary to the respiratory changes, since the accompanying blood pressure alterations give no indication of any severe asphyxia.

SUMMARY

This work was calculated to reproduce pathologic conditions taking place in cases of disease of the nervous system associated with hyperglycemia, in which either local mechanical compression of the medulla oblongata or general rise of the cerebrospinal fluid tension followed by compression of the whole central nervous system is essential.

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68. Gottschalk, Alfred; and Pohle, E.: Arch. f. exper. Path. u. Pharmakol. **95**:64-74, 1922.

69. Billigheimer, E.: Deutsch. Arch. f. klin. Med. **136**:1-32 (April) 1921.

70. Heténvi and Lax: Biochem. Ztschr. **125**, 1921.

71. Goetsch; Cushing, and Jacobson: Bull. Johns Hopkins Hosp. **22**:165-190, 1911; ibid. **24**:40, 1913.

72. Brugsch, T.; Dresel, and Lewy: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **34**:347, 1922.

73. Eppinger; Rudinger, and Falta: Ztschr. f. klin. Med. **66**:1-52, 1908; ibid. **67**:380-398, 1908.

The analogy consisted in applying local mechanical pressure on the medulla oblongata and general hydrostatic pressure on the whole central nervous system.

Both procedures, applied experimentally on cats, were followed by a rise in the sugar content of the blood.

Hyperglycemia, thus artificially produced in animals, represents in pertinent clinical cases a chronic type of piqûre, which may have several factors concerned in its causation.

Book Reviews

MEDICAL AND SURGICAL REPORT OF THE ROOSEVELT HOSPITAL, NEW YORK. Second series, 1925. Pp. 378; 47 illustrations. Cloth. Price, $5 net. New York: Paul B. Hoeber, 1925.

This is the second medical and surgical report of the Roosevelt Hospital; the first was published in 1915, and this number was to have been published in 1920 but was delayed because of the war. It contains articles on various topics by members of the staff. Some of the articles were written expressly for this report but many articles that have been published elsewhere are included.

The articles in this volume are on a wide variety of subjects and over half are contributed by a relatively small group of workers. Most of the articles are in the nature of case reports, statistical compilations or general discussions on some topic of universal interest. There is little evidence of medical research work contained in them. The illustrations are excellent and well reproduced.

This book should be of interest to a rather special group of medical men but would be of little if any value to the student and the general practitioner.

THE STOMACH AND UPPER ALIMENTARY CANAL IN HEALTH AND DISEASE. By T. IZOD BENNETT, Assistant Physician to the Middlesex Hospital and Physician to the Royal National Orthopaedic Hospital. Price, $6. New York: William Wood & Co.

The first five chapters of this book contain much practical information relative to conditions of the mouth, tongue, teeth, salivary glands, tonsils and pharynx. In the following chapter the various disorders of the esophagus are discussed briefly and their treatment is outlined. Eight chapters are devoted to the stomach. Its physiology is described and the pathology, symptoms and treatment of its organic and functional diseases are carefully considered. In the last three chapters of the book the author discusses aerophagy, undernutrition, and the rôle of hepatic and pancreatic disease in digestive disorders.

In all the book may be said to be well worth reading. It is designed for students and practitioners of medicine. It is extremely practical and concise, and is not overloaded with theory and detail. The indications for the surgical treatment of peptic ulcer are definitely listed as are those for the medical treatment in which the author enthusiastically recommends the method introduced by the late B. W. Sippy. Many of the old erroneous notions of gastro-intestinal disease are carefully dispelled. The book marks a definite advance in the literature of the gastro-intestinal tract and one feels regret that the author has not continued his discussion to include the lower part of the alimentary canal.